TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE

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DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled "**TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE**" submitted towards partial fulfillment of the requirements for the award of DM in Neurology degree to BFUHS is a compilation of original work carried out by me under the supervision of **Dr. Rajinder Bansal**, Professor, Department of Neurology, **Dr. Birinder Singh Paul**, Professor, Department of Neurology. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated

to

my Family

&

Teachers

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"The brain is like a muscle. When it is in use, we feel very good. Understanding is joyous"

- Carl Sagan, American Astrophysicist

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Dr. Parth Bansal

LIST OF ABBREVIATIONS

AHI-	Apnea- Hypopnea Index
avg.-	Average
CBGD-	Corticobasal Ganglionic Degeneration
DLB-	Dementia with Lewy Bodies
EF-	Executive Function
ESS-	Epworth sleepiness scale
FAB-	Frontal Assessment Battery
FTD-	Frontotemporal Dementia
H&Y-	Hoehn and Yahr score
ISCS-	inappropriate sleep composite score
MCI-	mild cognitive impairment
min.-	minimum
MMSE-	Mini-Mental State Examination
MSA-	Multiple System Atrophy
OSA-	Obstructive Sleep Apnoea
PD-	Parkinson's disease
PDSS-	Parkinson's disease sleep scale
PLMI-	Periodic Leg Movement Index
PSG-	Polysomnography
PSP-	Progressive Supranuclear Palsy

PSQI-	Pittsburgh sleep quality inventory
RBD-	rapid eye movement sleep behaviour disorder
REM-	rapid eye movement
RLS-	restless legs syndrome
SaO_{2-}	oxygen saturation
SCOPA-cog-	scales for outcomes in Parkinson's disease cognitive scale
SCOPA-	sleep- scales for outcomes in Parkinson's disease sleep scale
SRBD-	sleep related breathing disorders
SSS-	Stanford sleepiness scale
SWS-	slow wave sleep
UPDRS-	united Parkinson‟s disease rating scale

ABSTRACT

Introduction: Parkinson's Disease, a progressive neurological disease characterized by motor and non-motor symptoms. Non-motor symptoms include sleep-disorders which are less well studied, even lesser in atypical Parkinsonian Disorders. Present literature has used subjective sleep measurement and fewer have used polysomnography to compare them.

Aim: To study incidence and prevalence of sleep dysfunctions across atypical Parkinsonian Disorders and PD, and to compare sleep-disorders and PSG parameters amongst them.

Methods: All patients who had presented to the Neurology department of DMCH, Ludhiana from 1st-Mar-2020 till 31st-Dec-2021 were enrolled. Included were those with age ≥18 years and a diagnosis of PD/atypical Parkinsonian Disorders. Patients on sleep medications, drug-induced or vascular parkinsonism, with comorbidities like Diabetes, hypothyroidism were excluded. All patients underwent sleep-questionnaires including Epworth Sleep Scale, Parkinson's Disease Sleep Scale-2 and Restless Leg Syndrome rating scale. Consenting patients were subjected to polysomnography.

Results: Among 52 patients analysed, sleep dysfunctions were highly prevalent: 100% amongst atypical Parkinsonian Disorders and 76% in PD patients. Altogether 11 sleep-related complaints were considered. 5 complaints were found to be *significantly higher* in atypical Parkinsonian disorders, whereas *mood disturbance* was *significantly higher* in PD patients. Most common complaint in both the groups was insomnia. Excessive daytime sleepiness and breathing difficulty at night were more prevalent in MSA, early waking was seen exclusively in PSP, while dream enacting behaviour was mostly seen in DLB patients. All 3 clinical scores were significantly higher in atypical Parkinsonian Disorders. *ESS* was highest in MSA while *PDSS-2* and *RLS rating scale* were highest in CBGD patients. In PSG, three out of 12 parameters: *total sleep time, sleep efficiency* and *REM sleep%* were *significantly lower* while *N1 sleep%* was *significantly higher* in atypical Parkinsonian Disorders. Amongst them: *total sleep time, sleep efficiency and N1 sleep%* were lowest in MSA; *N2 and REM sleep%* were lowest in CBGD while *N3 sleep%* was lowest in PSP patients.

Conclusions: Sleep dysfunctions and PSG can help differentiate PD from atypical Parkinsonian Disorders in clinically ambiguous cases where there is diagnostic dilemma.

Key words: Parkinson's Disease, atypical Parkinsonian Disorders, ESS, PDSS-2, RLS rating scale, sleep dysfunctions, polysomnography.

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INTRODUCTION

Parkinson's Disease (PD) is a progressive neurological disease characterized by bradykinesia, resting tremors, rigidity, and, in more advanced phases, postural instability [1]. However, apart from these classical motor symptoms, there are non-motor symptoms which include sleep disorders, mood changes, dysfunctions of the autonomic nervous system, changes in sensory perception and cognitive deficits [1,2].

While there is a lot of literature discussing motor symptoms, non-motor symptoms, particularly sleep disorders in PD are not so avidly and frequently discussed. Notwithstanding, sleep problems are one of the major, challenging issues in patients with PD and affect a significant number of patients [1,3,4]. Disturbances in sleep physiology cause a reduction in the quantity and quality of sleep which thereby significantly affect their social functioning and quality of life. The most prevalent sleep disorder in PD is cited as insomnia, while others include REM sleep behaviour disorder (RBD) and obstructive sleep apnoea (OSA) [1,5].

REM sleep behaviour disorder (RBD) is one of the most common non-motor symptoms of PD and is characterized by the return of muscle tone during REM sleep and motor activities [6]. It may result in serious injury to patients with PD and their sleep partners but its exact clinical features, and the relationship between RBD and motor symptoms and other non-motor symptoms in patients with PD, are not well described. Recent studies demonstrated that inflammation beyond the SN correlates with non-motor symptoms of PD [7,8]. There is increasing evidence to suggest that microglial over activation has a pivotal role in PD progression [6,7]. α-Synuclein oligomer, which is pathologic hallmark of PD, can activate microglia and induce robust production of inflammatory factors, dopaminergic neurodegeneration and motor as well as non motor symptoms [6-9].

There are several tools to monitor sleep structure, one of which is PD sleep scale 2 (PDSS-2), a recently developed tool for screening and

managing sleep disturbance in PD patients. It consists of 15 items which are clinically relevant to nocturnal problems including non-motor and motor problems in PD. The PDSS-2, with an extended spectrum of nocturnal disabilities and easier use for patients, is a reliable, valid, precise, and potentially treatment-responsive tool for measuring sleep disorders in PD [10]. However, the gold standard for diagnosing sleep related disorders remains overnight polysomnography (PSG).

Apart from Parkinson's Disease (PD), sleep disorders are a frequent complication of the four Atypical Parkinsonian Disorders as well, which are Dementia with Lewy bodies (DLB), Multiple system atrophy (MSA), Progressive Supranuclear Palsy (PSP) and Corticobasal Ganglionic Degeneration (CBGD).

Dementia with Lewy bodies (DLB) is the third most common cause of dementia, and the typical clinical presentation is rapidly progressive cognitive impairment [11]. REM Behaviour Disorder (RBD) is one of the core features of DLB and may occur either before or simultaneously with the onset of DLB [12]. The prevalence of RBD in DLB is up to 76% [13]. Overall, the reported prevalence of sleep dysfunction in the DLB population ranges from 44% to 55% [14,15]. A recent study of PSG in 72 patients with DLB found that 96% had reports of dream enactment behaviour and 83% had REM sleep without atonia demonstrated on PSG. In addition, a large case series was conducted evaluating the clinical and neuropathologic diagnoses of 172 patients with RBD, which found that the most common diagnosis (45% of cases) was DLB [16].

Another type of atypical parkinsonian disorder is Multiple System Atrophy (MSA), which is a sporadic, adult-onset, progressive neurodegenerative disease characterized clinically by parkinsonism, cerebellar ataxia, autonomic failure, and corticospinal signs with poor or no response to levodopa. Pathologically, it is typified by cell loss, gliosis, and glial cytoplasmic inclusions in several neural cell systems (striatonigral, olivopontocerebellar, autonomic) [17]. Excessive daytime sleeping has been reported in 28%-50% of the MSA patients [18,19] while early wakefulness and insomnia has also been reported in 33% and 20% MSA patients respectively [17]. An analysis of polysomnography in

these patients showed reduced total sleep time and sleep efficiency [20–24], with one of these studies emphasised that sleep stages 1 and 2 were increased, while stages 3 and 4 decreased but REM sleep was normal [21].

OSA have been reported as the most common sleep-related breathing disorders in MSA patients [18,22-25] with prevalence ranging from 15% to 37% [21–23]. This may contribute to mild O2 desaturation occurring during sleep in MSA. RBD is the most common sleep-related disorder in MSA [18,20,23,25-27] and may precede the development of parkinsonism by years [22,27–29]. Clinical symptoms of RBD precede the onset of MSA by more than 1 year in 44% of the patients in some studies [21,23].

Progressive Supranuclear Palsy (PSP) is another atypical parkinsonian disorder, characterized by supranuclear ophthalmoplegia, postural instability, parkinsonism, and pseudobulbar palsy. It results from abnormal accumulation of tau, a microtubule-associated protein, resulting in neurofibrillary tangles. PSP is characterized by marked atrophy of the midbrain [30,31]. Abnormalities in sleep architecture and insomnia occurs frequently in PSP. Studies have reported decreased total sleep time, decreased sleep efficiency and REM sleep, along with a significant increase in the number and duration of night time arousals. These findings can be explained by the preferential degeneration of the pontine tegemental nuclei in the brainstem and its connections with the reticular nuclei of the thalamus, thought to be important for the generation of REM sleep [32,33].

Corticobasal Ganglionic Degeneration (CBGD) is an uncommon form of tauopathy characterized clinically by combination of both cortical and parkinsonian features [30]. Gross neuropathology is marked by asymmetric focal cortical atrophy, whereas the hallmark microscopic pathologic findings include ballooned neurons in the cortex and astrocytic plaques [34]. Due to its rarity, there is limited data on sleep disorders in CBD. Current literature is primarily limited to case reports. In a study of 5 patients with CBD, all 5 had insomnia, 4 had periodic limb movements during sleep, 2 had sleep disordered breathing, and none had symptoms suggestive of RBD [35].

Sleep disorders are common but under-reported problems in PD and atypical parkinsonism patients, and are underdiagnosed even by health professionals. Their understanding and diagnosis will allow for development of much needed treatment approaches for these non-motor manifestations. Majority of the studies have used subjective sleep measurement and there are very few studies on PSG diagnosed sleep disorders and sleep architecture patterns in these patients. Moreover, there are only anecdotal reports in literature of atypical parkinsonism patients regarding sleep disorders, possibly due to the limited number of patients in this cohort. There is also a lack of comparison among the four atypical parkinsonian disorders and to PD patients overall. In this study, we have combined subjective sleep measurement and PSG to determine sleep characteristics in PD and atypical parkinsonism patients, and compared the data amongst the various groups.

AIMS AND OBJECTIVES

- To study incidence and prevalence of sleep dysfunctions in the studied patient population with Atypical Parkinsonian Disorders and Parkinson's Disease.
- To compare sleep dysfunctions between Atypical Parkinsonian Disorders and Parkinson's Disease in the studied patient population.
- To compare sleep dysfunctions among various types of Atypical Parkinsonian Disorders.

REVIEW OF LITERATURE

As many as 98% of patients with PD may suffer at some time from nocturnal symptoms that can disturb their sleep [3]. A community-based study reported 60% of patients with PD (144 of 239) with sleep problems, compared with 33% of healthy controls (33 of 100) with the same age and sex distribution [36], whereas Karlsen *et al* [37] reported that 64% of patients with PD had a sleep disorder, compared with 33% of controls. A recent study in 123 PD patients across all age groups and 96 age-matched controls using a newly validated non-motor questionnaire for PD (NMSQuest) reported that sleep problems such as restless legs syndrome (RLS), excessive day-time sleepiness and rapid eye movement (REM) behaviour disorder (RBD) were highly significantly more common in PD patients compared with those in controls [38].

a. In 1995, Tan et al in their case series and brief report described three cases of Rapid Eye Movement (REM) sleep disorder, which was a recently characterised rare disorder at the time. They found all three cases associated with PD, and preceding its onset by 4-5 years, and when symptoms of PD worsened, they were prescribed levodopa, which interestingly helped in relief of sleep related symptoms as well. The authors explained this to be due to the fact that dopamine D_1 receptor influences REM sleep as did Serotonin, another neurotransmitter intimately involved in sleep (the main neurotransmitter for non-REM sleep and secondarily primes REM sleep). Levodopa stimulates dopamine D_1 receptors and reduced serotonin levels; both factors could lead to reduced REM sleep, thus suppressing RBD in these patients [39].

In 2001, Ondo et al published their 3-month questionnaire-based survey on 320 patients of PD, to evaluate Daytime sleepiness and other sleep disorders in Parkinson's disease. The authors collected demographic and medication data, and the patients completed the Epworth Sleepiness Scale (ESS), questions assessing the presence of restless legs syndrome (RLS), a modified National Sleep Foundation

sleep survey, and specific questions regarding falling asleep while driving. The mean age of the remaining 303 patients was 67.1 ± 10.7 years, and the mean duration of PD was 9.1 ± 5.7 years. The ESS scores averaged 11.1 ± 5.9, and in 50.2% of patients the score was abnormally high (>10). Stepwise regression analysis found that sleepiness correlated with longer duration of PD ($p < 0.001$), more advanced PD ($p < 0.004$), male sex ($p < 0.001$), and the use of any Dopamine Agonists (DA, $p < 0.003$). The soporific effects of the three most common DA (pramipexole, ropinirole, and pergolide) were similar [40].

The documentation of sleep-related problems associated with Parkinson's disease (PD) dates as far back as James Parkinson's original monograph about the disease: 'His attendants observed, that of late the trembling would sometimes begin in his sleep, and increase until it awakened him: when he always was in a state of agitation and alarm' [41].

A study conducted by Turner RS in 2002 showed that Idiopathic rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia clinically linked with the alpha-synucleinopathies multiple systems atrophy (MSA), Parkinson's disease (PD), and dementia with Lewy bodies (DLB). Available autopsy information is limited but suggests that the pathologic basis of idiopathic RBD may be neuronal loss and Lewy bodies in pigmented monoaminergic nuclei, including the locus coeruleus and substantia nigra, which project to pontine nuclei mediating atonia during REM sleep. Thus, idiopathic RBD may be an alpha-synucleinopathy per se and a harbinger of impending PD, DLB, or MSA [42].

Gagnon et al in 2002 studied the frequency of REM sleep behaviour disorder (RBD) among patients with PD using both history and polysomnography (PSG) recordings and REM sleep muscle atonia in PD. Consecutive patients with PD (n = 33) and healthy control subjects (n = 16) were studied. Each subject underwent a structured clinical interview and PSG recording. REM sleep was scored using a method that allows the scoring of REM sleep without atonia. One third of

patients with PD met the diagnostic criteria of RBD based on PSG recordings. Only one half of these cases would have been detected by history. Moreover, the percentage of time spent with muscle atonia during REM sleep was lower among patients with PD than among healthy control subjects (60.1% vs 93.2%; $p < 0.003$). All these findings led them to conclude that RBD and REM sleep without atonia are frequent in PD as shown by PSG recordings. They suggested future studies should also investigate the relative importance of increased phasic EMG activity and loss of muscle atonia in establishing the diagnosis of RBD [43].

Another study conducted by Hasegawa et al in 2004 showed that approximately 74-94% patients with Parkinson's disease have sleep disorders: such as frequent awakening, excessive daytime sleepiness, nightmares, nocturnal cramps, REM sleep behaviour disorders and so on. In contrast, the relationship between physiological mechanism of sleep and the dopamine systems are still obscure, because the dopamine systems are not directly related neither initiating or maintaining sleep system nor awaking system. However, most of all the dopaminergic drugs were reported to induce sleepiness or sleep attacks in the patients with Parkinson's disease [44].

De Cock VC et al in 2008 showed that altered sleep and vigilance are among the most frequent symptoms, besides parkinsonism, in movement disorders. As many as 60% of patients with Parkinson's disease (PD) experience insomnia, 15-59% show rapid eye movement (REM) sleep behaviour disorders (RBDs), and 30% show excessive daytime sleepiness RBDs are thought to be caused by lesions in the REM sleep atonia system, and can, in association with other early markers of neurodegenerative diseases, such as olfactory, cognitive and autonomic disturbances, precede parkinsonism by several years. Daytime sleepiness, often with a narcolepsy-like phenotype, is a common occurrence in PD, owing to lesions in the arousal systems of the brain. The use of dopamine agonists increases the risk of sleep attacks, especially when driving, suggesting a drug-disease interaction [45].

Another study conducted by Arnulf I et al in 2009 showed that excessive daytime sleepiness is a disabling and vital problem in patients with PD. It affects around 33% patients and culminates in sleep attacks (without prodroma) in 1 to 4% of the patients. When monitored, short, narcolepsy-like naps with abnormal intrusion of REM sleep during daytime (and hypnagogic hallucinations as wakeful dreams) are observed in 33-41% patients, while other patients display naps with non-REM sleep. Although insomnia, sleep apnoea and periodic leg movements are common in these patients, there is no clear link between the night events and the level of sleepiness. Patients treated with dopamine agonists are two to three-fold more exposed to sleep attacks than those on levodopa, with large variability between patients. Sleepiness may exist, to a lesser degree, before the onset of parkinsonism and before the use of dopamine agents, suggesting that other, disease-dependant factors contribute to the sleepiness [46].

Uemera et al in 2009 evaluated whether the PD sleep scale (PDSS) is a valid method to analyze sleep disturbance in 79 PD patients, compared to an equal number of matched controls. They compared the PDSS with other questionnaires such as the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). They analyzed the correlation between the results of the PDSS and the PSQI, since PSQI was developed for evaluation of insomnia in the general population and might be insufficient to evaluate sleep disturbances in patients with PD. The total PDSS score was also analyzed whether PDSS was correlated with sleep efficiency as measured by PSG. They found significant internal consistency using the PDSS, validating it as an accurate scale for sleep disturbances. The total PDSS strongly correlated with sleep efficiency in PSG which suggested that the total scores of the PDSS reveal sleep disturbances in patients with PD and hence they recommended that the PDSS total score cut-off point for detecting sleep disturbances should be set at 120 points and proposed that the PDSS is useful for screening and estimating sleep disturbances in PD patients without the need for PSG recordings [47].

A comparative study performed by L. Gama et al in 2009 studied sleep

disturbances and brain MRI morphometry in Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). This was a cross-sectional study of 16 PD cases, 13 MSA, 14 PSP and 12 control. Sleep disturbances were evaluated by Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index (PSQI), Restless Legs Scale and Berlin questionnaire. Pons area, midbrain area, medial cerebellar peduncle (MCP) width, and superior cerebellar peduncle width were measured using MRI. Poor quality sleep, risk of obstructive sleep apnoea (OSA) and restless legs syndrome (RLS) were detected in all groups. Patients with MSA showed higher risk of OSA and less frequent RLS. In MSA, a correlation between PSQI scores and Hoehn and Yahr stage was observed ($p < 0.05$). In PSP, RLS was frequent (57%) and related with reduced sleep duration and efficiency. In PD, excessive daytime sleepiness was related to atrophy of the MCP ($p=0.01$). RLS was more frequent in PD and PSP, and in PSP, was associated with reduced sleep efficiency and sleep duration. Brain morphometry abnormalities were found in connection with excessive daytime sleepiness and risk of OSA in PD and PSP suggesting widespread degeneration of brainstem sleep structures [48].

The movement disorder society commissioned a task force in 2010 to examine the variety of scales applied to the evaluation of PD sleep and wakefulness and to assess their use in PD. A systematic literature review was conducted to explore the use of sleep scales in PD and to determine which scales qualified for a detailed critique. The task force mem- bers, all of whom had extensive experience in assessing sleep in PD reviewed each of the scales using a structured proforma. A total of 48 potential scales were identified, 29 were excluded because they did not meet review criteria or were variations of scales already included, leaving 19 scales that were critiqued and rated. Only six were found to meet criteria for recommendation or suggestion by the task force: the PD sleep scale (PDSS) and the Pittsburgh sleep quality index (PSQI) were recommended for rating overall sleep problems to screen and to measure severity, the SCOPA-sleep (SCOPA) was recommended for rating overall sleep problems both to screen and to measure severity,

and for rating daytime sleepiness; the Epworth sleepiness scale (ESS) was recommended for rating daytime sleepiness to screen and to measure severity; the inappropriate sleep composite score (ISCS) was suggested for rating severe daytime sleepiness or sleep attacks to screen and to measure severity; and the Stanford sleepiness scale (SSS) was suggested for rating sleepiness and to measure severity at a specific moment. The task force discussed each of the scales in detail and did not recommend the development of new scales, but emphasized the need for educational efforts to train physicians in sleep interview techniques and polysomnography (PSG). They added as an addendum that recently, the PDSS had been revised and the new version, PDSS-2, had been validated by the Movement Disorder Society [49].

Trenkwalder et al validated the PDSS-2 as a reliable, valid, precise, and potentially treatment-responsive tool for measuring sleep disorders in PD, with an extended spectrum of nocturnal disabilities and easier use for patients, in their landmark publication the following year [16]. Since the previous Parkinson's disease sleep scale (PDSS) was a 15-item visual analogue scale that assessed the profile of nocturnal disturbances in PD patients, it was decided to extend the scale so that it becomes a frequency measure scale with five categories and encompasses unmet needs such as restless legs syndrome, akinesia, pain, and sleep apnoea. For validation of the PDSS-2, PD patients' ratings and investigators' interviews were compared to ratings from a semi structured interview with a caregiver/partner, and to related scales. PDSS-2 was repeated for test-retest-reliability after 1–3 days. A total of 113 PD patients showed a mean (SD) total score of 16.5 (68.9) (range: 2–40) indicating mild to moderate sleep disturbances. PDSS-2 item-total correlation for proving internal consistency was satisfactory (correlations >0.30). From a factor analysis, three subscales were derived: (1) ‘‘motor problems at night,’’ (2) ‘‘PD symptoms at night’’ and (3) ‘‘disturbed sleep.’’ The alpha coefficient for the total score was 0.73, for subscales 0.47 to 0.66. The test-retest-reliability intra-class-coefficient for the total score was 0.80, with 0.69 and 0.77 within the

subscales. For discriminative validity, significant differences were found in the PDSS-2 total score depending on CGI and Hoehn and Yahr severity levels. A comparison between caregivers' and patients' ratings was carried out with a successful outcome [50].

Postuma et al made another attempt to predict the course of the disease in their longitudinal cohort study of RBD patients in 2010 by identifying those who had developed neurodegenerative disease, matching these by age, sex, and follow-up duration to patients with RBD who remained disease-free and to controls; and compared polysomnographic (PSG) variables at baseline (i.e., before development of neurodegenerative disease) between groups. Twenty-six patients who developed neurodegenerative disease were included (PD 12, multiple system atrophy 1, dementia 13). The interval between polysomnogram and disease on- set was 6.7 years, mean age was 69.5, and 81% were male. There were no differences between groups in sleep latency, sleep time, % stages 2–4, % REM sleep, or sleep efficiency. However, patients with idiopathic RBD who developed neurodegenerative disease had increased tonic chin EMG activity during REM sleep at baseline compared to those who remained disease-free (62.7 $\pm$ 6.0% vs 41.0 $\pm$ 6.0%, p=0.020). This effect was seen only in patients who developed PD (72.9 $\pm$ 6.0% vs 41.0 $\pm$ 6.0%, p=0.002), and not in those who developed dementia (54.3 $\pm$ 10.3, p=0.28). There was no difference in phasic submental REM EMG activity between groups. Hence, they concluded that in patients with REM sleep behaviour disorder initially free of neurodegenerative disease, the severity of REM atonia loss on baseline polysomnogram predicts the development of Parkinson disease (PD) [51].

Another study conducted by Nomura T et al in 2012 showed that PSP patients had more severe symptoms of Parkinsonism and cognitive impairment, and took lower doses of dopaminergic agents compared with PD patients. The PSP group had lower values for both estimated total sleep time and sleep efficiency on PSG compared with the PD group ($p = 0.002$, $p = 0.021$, respectively). The PSP group also included a significantly smaller number of patients having REM sleep

without atonia (RWA) compared with the PD group (n = 5, 20.0% vs. n = 56, 60.2%, p = 0.003). None of the PSP patients were experiencing RBD-related symptoms at the time of the investigation, while 30 PD patients (32.3%) had RBD-related symptoms [52].

For studying the prevalence and profile of Restless Legs Syndrome (RLS) in Parkinson's disease (PD) and other neurodegenerative disorders (MSA, PSP and DLB): A case-control study was performed by Bhalsing et al on 187 consecutive patients with parkinsonian disorders (PD=134, PSP=27, MSA=21, DLB=5) and 172 healthy controls. RLS was diagnosed using the International RLS Study Group (IRLSSG) criteria and the severity of RLS was assessed in patients with definite RLS. Quality of sleep was evaluated with established scales. The prevalence of RLS was higher in patients compared to controls (9.6% vs. 2.9%; p=0.009) and was highest in PD (11.9%). RLS was present in only one patient each with MSA and PSP and none with DLB. The mean IRLSSG severity score of patients was 16.2±6.5. The global Pittsburgh Sleep Quality Index score and Epworth Sleepiness Scale score were significantly higher in patients compared to controls (p < 0.001). PD patients with RLS had lower PDSS score compared to patients without RLS (p = 0.023). There was no significant difference in gender, age, duration and severity of PD between the two groups. Thus, their study found a higher prevalence of RLS in PD compared to healthy controls or other parkinsonian disorder but apart from PDSS score, there was no significant difference in the clinical characteristics of PD patients with and without RLS [53].

In a questionnaire survey, Di Fabio et al identified 36 (9%) of 417 Parkinson's disease (PD) patients with sleep- walking (SW); 72% of them also had a history of REM sleep behaviour disorder (RBD). They then aimed to assess the clinical and polysomnographic characteristics of SW in PD and to compare them to patients with PD with and without a history of RBD. They performed video-polysomnography (Video-PSG) and detailed clinical examination in 30 PD patients from the above-mentioned survey: 10 patients with a history of SW, 10 patients with a history of RBD, and 10 patients with no history of either SW or

RBD and found that PD patients with SW had higher depression, anxiety and Hoehn & Yahr scores and lower activities of daily living scores than patients without a history of RBD but did not differ from patients with RBD. Patients with SW and RBD also had more often dyskinesia and hallucinations. By PSG, RBD was observed in 8 patients with SW and in all patients with a history of RBD. A total of 5 patients without a history of either SW or RBD had REM sleep without atonia without behavioural peculiarities. They concluded that the simultaneous occurrence of SW and RBD (overlap parasomnia) in most patients suggested a common underlying disturbance of motor control during sleep in PD, with variable manifestations in different sleep stages [54].

Since daytime and nighttime sleep disturbances and cognitive impairment occur frequently in PD, but little is known about the interdependence of these non-motor complications. Thus, Goldman et al in 2013 examined the relationships among excessive daytime sleepiness, nighttime sleep quality and cognitive impairment in PD, including severity and specific cognitive deficits. Ninety-three PD patients underwent clinical and neuropsychological evaluations including the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). Patients were classified as having normal cognition (PD-NC), mild cognitive impairment (PD-MCI), or dementia (PDD) using recently proposed Movement Disorder Society PD-MCI and PDD criteria. Relationships between the sleep and cognitive measures and PD cognitive groups were examined. The PD cohort included PD-NC (n=28), PD-MCI (n=40), and PDD (n=25) patients. ESS scores, as a measure of daytime sleepiness, were significantly worse (p=0.005) in cognitively impaired PD patients, particularly PDD patients. ESS scores correlated significantly with Mini-Mental State Examination scores and also with cognitive domain scores for attention/working memory, executive function, memory, and visuospatial function. In contrast, PSQI scores, as a measure of night-time sleep quality, neither differed among cognitive groups nor correlated with any cognitive measures. Hence, they concluded that

daytime sleepiness, not night-time sleep problems, is associated with cognitive impairment in PD, especially in the setting of dementia, and attention/working memory, executive function, memory, and visuospatial deficits [55].

Sabra M. Abbott et al in 2014 showed that sleep disorders are commonly observed in Atypical Parkinsonism, with particular disorders occurring more frequently in specific parkinsonian disorders. Multiple system atrophy (MSA) is a synucleinopathy often associated with nocturnal stridor, which is a serious, but treatable, condition highly specific to MSA. In addition, this disorder is strongly associated with rapid eye movement sleep behaviour disorder (RBD), which is also observed in dementia with Lewy bodies. RBD is far less prevalent in progressive supranuclear palsy (PSP), which is a tauopathy. Insomnia and impaired sleep architecture are the most common sleep abnormalities observed in PSP. Corticobasilar degeneration is also a tauopathy, but has far fewer sleep complaints associated with it than PSP [30,61].

Since sleep disturbance is a common nonmotor phenomenon in Parkinson's disease (PD) affecting patient's quality of life, Martinez-Ramirez in their study examined the association between clinical characteristics with sleep disorders and sleep architecture patterns in a PD cohort from June 2009 to May 2013. Patients underwent a standardized PSG in their "on medication" state. They observed that male gender($p=0.02$) and disease duration (<5 years) were independently associated with obstructive sleep apnoea (OSA). Only lower levodopa equivalent dose (LED<600 mg) was associated with periodic limb movement disorders (PLMD). REM sleep behaviour disorder (RBD) was more common among older patients, with higher MDS-UPDRS III scores ($\geq$25), and LED($\geq$1000mg). None of the investigated variables were associated with the awakenings/arousals (A/A). Sleep efficiency was predicted by amantadine usage and age, while sleep stage 1 was predicted by dopamine agonists and Hoehn & Yahr severity. The use of MAO-B inhibitors and MDS-UPDRS part III were predictors of sleep stages 2 and 3. Age was the only predictor of

REM sleep stage and gender for total sleep time. They concluded that sleep disorders and architecture are poorly predictable by clinical PD characteristics and other disease related factors must also be contributing to these sleep disturbances [56].

In a cross-sectional analysis of 636 adult PD patients compared to 143 age and sex- matched non-PD control patients, Ratti et al assessed insomnia symptoms and other sleep features by the Pittsburgh Sleep Quality Index (PSQI), a global score > 5 defining impaired sleep. They found sleep dysfunction and insomnia symptoms to be more frequent in PD patients compared to control patients (63 vs. 45%, p=0.001). Female gender, duration of PD, presence of depression and anxiety were associated with the presence of insomnia in PD. Subjective sleep efficiency, habitual sleep quality, sleep disturbance and daytime dysfunction, but not sleep latency, were reduced in PD patients compared to controls. So, they concluded that the prevalence of sleep dysfunction was higher in PD than in other general medical conditions and insomnia in PD seems to affect sleep maintenance and not sleep onset [57].

A systematic review and meta-analysis performed by Pushpanathan et al in 2016 scanned 2283 articles initially and 16 studies met inclusion criteria. Across these 16 studies, there were 1882 people with PD. The average age was 66.28±8.65 years, and the average time since diagnosis was 7.17±6.04 years. All studies were conducted in a clinical setting. Mean united Parkinson's disease rating scale (UPDRS) scores were provided for 10 studies, while either mean or median Hoehn and Yahr (H&Y) scores were reported in 8. Six of the included studies used PSG, one relied on actigraphy while the rest used clinical outcomes alone. They reported that the results of this meta-analysis revealed significant effects of sleep problems on neuropsychological performance in PD across several cognitive domains. Most affected are the sub-domains of executive function, that is: shifting, updating, generativity and fluid reasoning and long-term verbal recall and long-term verbal recognition, both subdomains of memory [58].

Since Obstructive Sleep Apnoea Syndrome (OSAS) and other sleep-

disordered breathing (SDB) with Parkinson's disease (PD) had been reported in some small studies, Crosta et al to investigated the occurrence of SDB in a large consecutive outpatient series. It was a case-control study in subjects attending a neurological clinic between January 2010 and April 2013 where all patients were screened for SDB by means of sleep-wake history, Epworth Sleepiness Scale (ESS), and full-night polysomnography (PSG), when indicated. 3194 patients were recruited. Of these, 194 were affected by PD and 77 by other parkinsonism. Snoring, excessive daytime sleepiness and OSAS were more common in patients with PD or parkinsonism (40.59, 5.9, and 4.06%) than in controls (35.58, 2.19, and 2.09%). Their study suggested an increased frequency of OSAS and other SDB in PD and parkinsonism and hence they suggested for early detection and management of these disorders as they may have a substantial impact on quality of life and survival in these patients [59].

Corroborating with this study, Sobreira-Neto et al performed a cross-sectional study involving 88 consecutive patients with PD from out-patient clinic to determine the frequency of major sleep disorders in patients with Parkinson's disease (PD), diagnosed according to the third international classification of sleep disorders, and assess the relationship of those disorders with the quality of life. Participants were subjected to clinical interviews, assessment using standardized scales (Epworth Sleepiness Scale, PD Questionnaire, Pittsburgh sleep quality index (PSQI) and, for individuals with a diagnosis of RLS/ WED, International RLS/WED grading scale), and video-poly-somnography. They observed sleep disorders in 96.5% of the participants, with REM-sleep behaviour disorder found in 62.5%, obstructive sleep apnoea in 62.5%, insomnia in 55.7%, and restless legs syndrome in 28.4%. They also observed a correlation between health-related quality of life with the PSQI and the Epworth sleepiness scale, concluding that patients with PD have a high prevalence of sleep disorders and the quality of sleep and excessive daytime sleepiness significantly affects the quality of life in these individuals [1].

Another study conducted by Koo DL et al in 2018 showed that among

the 92 patients with RBD, 35 had iRBD, 25 had PD-RBD, 17 had MSA-RBD, and 15 had DLB-RBD. The mean apnoea-hypopnea index of atypical parkinsonism with RBD (AP-RBD) group was 16.2 ± 17.7 events/h (MSA-RBD, 14.0 ± 16.6; DLB-RBD, 18.8 ± 19.1), which was significantly higher than the other groups ($p < 0.05$). The proportion of patients with 100% supine sleep in the AP-RBD group (44%) was higher than that in the iRBD group (14%; $p=0.030$). The proportion of OSA with 100% supine sleep position was significantly higher in the MSA-RBD and DLB-RBD groups than in the iRBD group ($p = 0.042$ and $p=0.029$, respectively) [60].

In a review article by Chan et al, they commented that compelling evidence has suggested that both DLB and RBD are possibly caused by underlying synucleinopathy, and RBD often precedes DLB. Currently, the mainstay of pharmaco- logical treatment of RBD is clonazepam and melatonin, which may reduce the possibility of sleep-related injuries. As a sentinel of possible DLB and other synucleinopathy, RBD may be the beginning of degenerative diseases and pro- vide opportunities for preemptive treatment for earlier disease-modifying therapy, targeting α-synuclein or its regulatory pathways. Further studies need to address factors that will determine its phenoconversion to different types of synucleinopathy. Early interventional strategies should be developed to prevent or at least delay the consequences of devastating dementia, parkinsonism, and autonomic failures [11].

In a 2021 publication by Shin et al, they studied association of excessive daytime sleepiness with Parkinson's disease in late-life and with parkinsonian-like (P-L) symptoms in middle age. Since neurodegeneration can appear decades before a diagnosis of Parkinson's disease, identifying clinical features associated with this early progression is important. The purpose of this study was to determine the association of daytime sleepiness with P-L symptoms in a population-based sample of middle-aged Korean adults. During 2013 and 2014, daytime sleepiness and P-L symptoms were assessed in 2,063 males and females aged 50–64 years who were participating in

the Korean Genome and Epidemiology Study. The severity of daytime sleepiness was quantified by the score on the Epworth Sleepiness Scale (ESS). Self-reported P-L symptoms included nine motor disorders commonly associated with Parkinson's disease. The prevalence of excessive daytime sleepiness (ESS score >10) was 7.0%. The frequencies of P-L symptoms ranged from 0.5% (for "trouble buttoning buttons") to 18.4% (for "handwriting smaller than it once was"). After adjustment for covariates and multiple testing, the relative odds of P-L symptoms comparing the 80th and 20th percentiles of ESS scores was 1.6 (p=0.001) for "voice is softer than it once was," 2.1 (p<0.001) for "balance when walking is poor," and 1.5 (p=0.002) for "loss of facial expression." The prevalence of excessive daytime sleepiness increased from 6.3% to 19.8% when the number of symptoms increased from zero to three (p=0.004). They concluded that in Korean adults aged 50–64 years, daytime sleepiness was significantly associated with P-L symptoms. Whether coexisting daytime sleepiness and P-L symptoms predate extrapyramidal and other impairments in later life warrants further investigation [61].

MATERIALS AND METHODS

This cross-sectional, non-blinded observational study has been conducted to know the various sleep dysfunctions in Indian patients with atypical Parkinsonian Disorders and Parkinson's Disease.

All follow up and newly diagnosed patients of these diseases who had presented to the Neurology department of Dayanand Medical College and Hospital (DMCH), Ludhiana from 1st March 2020 till 31st December 2021 were enrolled for study after taking informed and written consent.

INCLUSION CRITERIA:

Any patient who had presented to DMCH in-patient/ outpatient clinic who were:

1. Age 18 years or above.
2. Had a Clinical diagnosis of Parkinson's disease using UK Parkinsons Disease Brain Bank criteria [62].

UK PARKINSON'S DISEASE BRAIN BANK CRITERIA
Step 1: Diagnosis of Parkinsonian Syndrome • Bradykinesia • 1 or more of ◦ rigidity ◦ rest tremor ◦ postural instability
Step 2: Absence of the following exclusion criteria • Repeated strokes with stepwise progression of Parkinsonism • History of repeated head injury • History of definite encephalitis • Oculogyric crisis • Neuroleptic treatment at symptom onset • More than one affected relative • Sustained remission of symptoms

- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language and praxis
- Babinski sign
- Presence of cerebral tumor or communicating hydrocephalus on brain imaging
- Negative response to large doses of Levodopa in absence of malabsorption
- MPTP exposure

Step 3: Supportive Criteria for Parkinson's Disease- 3 or more of the following required:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistant asymmetry affecting side of onset most
- Excellent response (70-100%) to Levodopa
- Severe Levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

3. Features of possible or probable Progressive Supranuclear Palsy were defined as [63]:

Probable PSP: vertical supranuclear palsy and prominent postural instability with falls within 1st year of disease onset

Possible PSP: either vertical supranuclear palsy or both of:

1. slowing of vertical saccades and
2. postural instability with falls within 1st year of disease onset

For both possible and probable PSP disease onset should be at age of 40 or later and the disorder should be progressive in nature

<table>
<tr><th colspan="3">Clinical and Imaging features of Multiple System Atrophy [64]</th></tr>
<tr><td colspan="3">Sporadic, progressive, adult (>30 y)- onset
Motor impairments + Autonomic failure+ Additional features</td></tr>
<tr><td>Motor impairment</td><td>Autonomic failure (moderate)</td><td>Additional features</td></tr>
<tr><td>Parkinsonism
Tremor
Bradykinesia
Rigidity
Postural instability</td><td rowspan="3">Urinary urgency
Urinary frequency
Incomplete bladder emptying
Erectile dysfunction in males
Significant OH that does not meet the level required in probable MSA</td><td><u>MSA-P</u>
Rapidly progressive Parkinsonism
Poor response to levodopa
Postural instability within 3 y of onset
Gait ataxia, cerebellar dysarthria, Limb ataxia or cerebellar oculomotor dysfunction
Atrophy on MRI of putamen, middle cerebellar peduncle (MCP), pons or cerebellum
Hypometabolism on FDG-PET in putamen, brainstem or cerebellum</td></tr>
<tr><td rowspan="2">Cerebellar Ataxia
Gait ataxia with cerebellar dysarthria
Limb ataxia
Cerebellar oculomotor dysfunction</td><td><u>MSA-P or MSA-C</u>
Stridor
Babinski sign with hyperrelexia</td></tr>
<tr><td><u>MSA-C</u>
Parkinsonism (bradykinesia and rigidity)
Atrophy on MRI of putamen, MCP or pons
Hypometabolism on FDG-PET in putamen
Presynaptic DA denervation on SPECT or PET</td></tr>
</table>

4. Features of Dementia with Lewy Bodies [65]

Features of Dementia with Lewy Bodies
Diagnosis requires • ≥ 2 core features or • 1 core feature plus one suggestive feature
Core features • Fluctuating cognition • Recurrent visual hallucinations • Parkinsonism
Suggestive Features • REM sleep behaviour disorder • Severe neuroleptic sensitivity • Low dopamine activity in basal ganglia on dopamine transporter SPECT or PET

5. Features of Corticobasal Ganglionic Degeneration defined as [66]:

Corticobasal Degeneration (CBD) Criteria	
Core Features	**Supportive Features**
Cortical dysfunction • Asymmetric ideomotor apraxia • Alien limb phenomenon • Visual or sensory hemineglect • Focal or asymmetric myoclonus • Non-Fluent Aphasia (overlap with PNFA)	• Lateralized cognitive dysfunction with preserved memory and learning • MRI with asymmetric atrophy in parietal and frontal cortex • FDG-PET decreased glucose uptake in parietal and frontal cortex, basal ganglia and thalamus
Extrapyramidal dysfunction • Asymmetric rigidity lacking levodopa response, and focal dystonia	

6. Patients of atypical parkinsonian disorders and parkinson's disease will be subjected to Sleep Questionnaires including
    a. Epworth Sleep Scale
    b. Parkinson's Disease Sleep Scale-2
    c. Restless Leg Syndrome Rating Scale (if required)

EXCLUSION CRITERIA

1. Patients on Sleep medications
2. Diabetes Mellitus
3. Hypothyroidism
4. Drug induced Parkinsonism
5. Vascular Parkinson's disease

Spectrum of sleep disorders associated with parkinson's disease:

1. *REM Sleep Behaviour Disorder (RBD):* In the Braak schema, involvement of the pathologic process in PD affects the SLD (sublaterodorsal nucleus), the magnocellular reticular formation (MCRF), and the perilocus coeruleus alpha structures as early as Stage 2. RBD is characterized by persistence of muscle tone during REM sleep accompanied by motor/ behavioural activity and dreaming [67].
2. *Excessive Daytime Sleepiness:* Excessive daytime sleepiness, defined as inappropriate and undesirable sleepiness during waking hours, is one of the most commonly reported sleep complaints in patients with PD, affecting between 15% and 50% of PD patients. The degree of EDS has been shown to be a key determinant of these patients' quality of life. The severity of EDS in patients with PD has been shown to increase with disease severity and disease duration [3].
3. *Restless Legs Syndrome and Periodic Limb Movements:* Restless legs syndrome (RLS) is a common neurologic disorder that affects 4%–10% of the general population. The pathophysiology is not clear-cut but it has been associated with iron deficiency and impairment of cerebral dopaminergic systems. The generally

accepted frequency is 10%–20% association of RLS symptoms in patients with PD [68].

4. *REM Sleep and Hallucinations:* F´enelon et al. showed that three factors were independently predictive of visual hallucinations: severe cognitive impairment, duration of PD, and daytime sleepiness. The association of RBD has been found to increase the risk of hallucinations by a factor of 3 [69].
5. *Sleep-Disordered Breathing:* The reported frequency of sleep-disordered breathing (SDB) in PD varies from 20% to 60%. Possible etiologic explanations include decrease in upper airway muscle tone because of degeneration of the brainstem serotoninergic neurons that innervate the muscles of the upper airway, deficient respiratory muscle coordination, or autonomic dysregulation [70].

Spectrum of Sleep disorders associated with atypical Parkinsonian disorders: In contrast to PD, sleep disorders in atypical parkinsonian syndromes, such as Multiple system atrophy (MSA), dementia with Lewy Bodies (DLB), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), have not been systematically studied. Sleep dysfunction can frequently be observed in these patient populations.

1. **Multiple system atrophy (MSA)** is a neurodegenerative disorder characterized by a combination of autonomic dysfunction, parkinsonism, and/or ataxia. Obstructive sleep apnoea (OSA) can be observed, but there are also case reports of central apnoeas occurring as the first symptom of MSA. Nocturnal stridor is one of the most serious sleep disorders associated with MSA [64].

Excessive daytime sleepiness (EDS) has been reported in 28% of Caucasian patients with MSA and 24% of Japanese patients with MSA. One of the hallmark symptoms of MSA is a loss of the normal nocturnal dip in blood pressure which appears to be much more pronounced in patients with MSA, compared to PD [20,71]

2. **Dementia with Lewy Bodies (DLB) -** the strong association between RBD and DLB prompted the inclusion of RBD as a core

clinical feature for the diagnosis of DLB in 2011.Excessive daytime sleepiness is seen in 75% cases of DLB [65].

3. **Progressive supranuclear palsy (PSP)** PSP patients has significantly decreased total sleep time and REM sleep, along with a significant increase in the number and duration of nocturnal awakenings. REM sleep without atonia and RBD are seen in 33% of PSP patients [63].
4. **Corticobasaldegeneration(CBD)** – Sleep disorders in CBD patients includes insomnia, periodic limb movements during sleep, sleep disordered breathing. Interestingly, periodic limb movements are seen more severe on the side dominantly affected by parkinsonism [66].

STATISTICAL METHODS:

The homogeneity of the demographic variables and the indicated clinical parameters were analyzed during the study. The description was made using the mean, median, range and standard deviation of the quantitative variables, as well as with the absolute frequency and relative frequency of the qualitative variables. The qualitative variables were analyzed using homogeneity tests based on the $\chi 2$ distribution when the expected values made this possible and using Mann-Whitney U, Wilcoxon W and Z tests, otherwise. Statistical significance was considered p values <0.05. They were analyzed using the Strata 14 software.

OBSERVATIONS AND RESULTS

All patients who had visited the Neurology department of Dayanand Medical College and Hospital (DMCH), Ludhiana either with the diagnosis of Parkinson's Disease (PD) or atypical Parkinsonian Disorders had been included in the analysis. Ninety-one (91) patients met the inclusion criteria. Out of these, 39 patients were excluded as 26 were diagnosed cases of Diabetes Mellitus, 4 had hypothyroidism, 6 were on sleep medications and 3 had been suffering from drug induced parkinsonism [Figure 1].

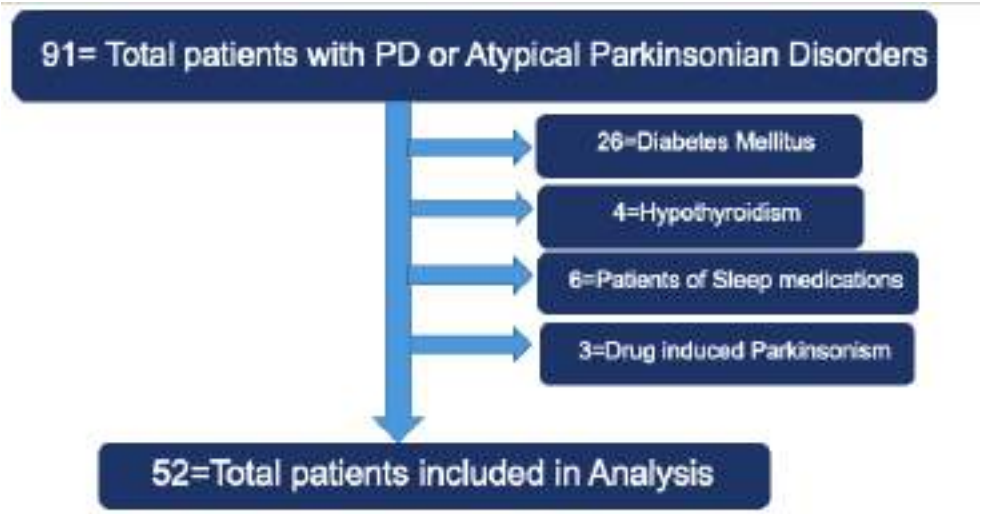
91= Total patients with PD or Atypical Parkinsonian Disorders
26=Diabetes Mellitus
4=Hypothyroidism
6=Patients of Sleep medications
3=Drug induced Parkinsonism
52=Total patients included in Analysis

Figure 1: Flow Diagram

The remaining 52 patients were included and then analysed and in the final cohort. Of these 52 patients, 29 patients (56%) were diagnosed as Parkinson's Disease (PD) while 23(44%) had atypical Parkinsonian Disorders {Figure 2}.

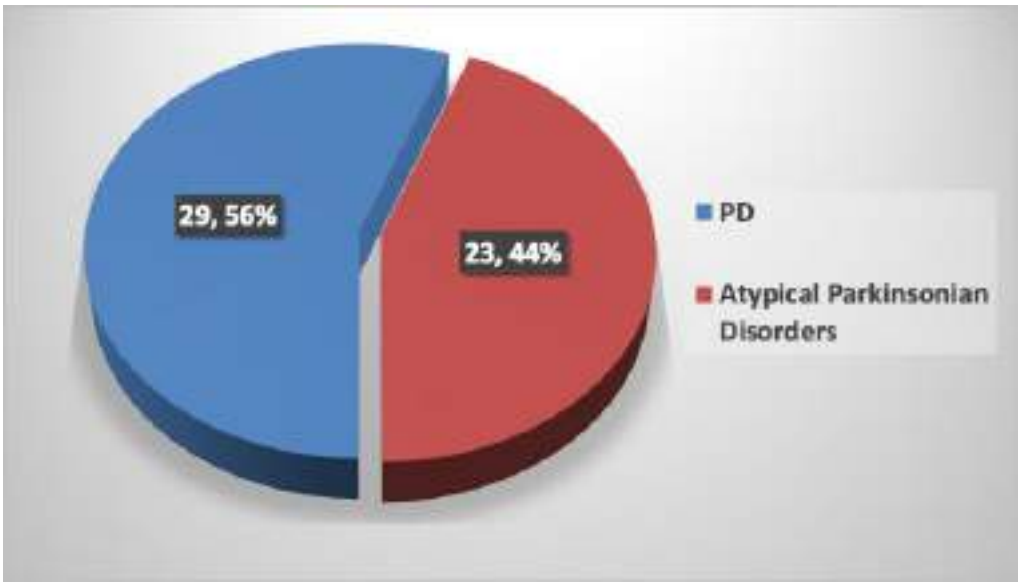

Figure 2: Patient Distribution in the total cohort

Among the 23 patients who had atypical Parkinsonian Disorders, there were 9 patients of Progressive Supranuclear Palsy (PSP) {39%}, 5 patients each of Corticobasal Ganglionic Degeneration (CBGD) and Multiple System Atrophy (MSA) {22%} and 4 patients of Dementia with Lewy Bodies (DLB) {17%}.

DEMOGRAPHIC DETAILS:

AGE DISTRIBUTION:

Patients with Parkinson's Disease (n=29):

Among the 29 patients diagnosed with PD, the mean age was **57.24**± 11.69 years (32-78 years) {Table 1}. Seven patients were aged less than 50 years, 18 had age between 51 and 70 years, while only 4 patients were more than 70 years.

Patients with atypical Parkinsonian Disorders (n=23):

Among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean age was **66.87**± 7.50 years (56-87 years). None of these patients had age less than 50 years, 17 had age between 51 and 70 years, while 6 patients were more than 70 years. For the 9 patients of PSP, the mean age was **66.44** ± 6.71 years (56-75 years); for the 5 patients of CBGD, the mean age was **64.40** ± 7.70 years (57-76 years) while for the 5 patients of MSA, the mean age was **65.00** ± 6.40 years (56-72 years) and for the 4 patients of DLB, the mean age was **73.25** ± 9.36 years (66-87 years) {Table 1}.

Table 1: Age Distribution in the total cohort

	Disorder	n	Mean	Standard Deviation	Minimum	Maximum
AGE (years)	PD	29	57.24	11.69	32.00	78.00
	PSP	9	66.44	6.71	56.00	75.00
	CBGD	5	64.40	7.70	57.00	76.00
	DLB	4	73.25	9.36	66.00	87.00
	MSA	5	65.00	6.40	56.00	72.00
	Total	52	61.50	11.07	32.00	87.00

GENDER DISTRIBUTION:

In the 29 patients diagnosed with PD, 9 patients were females (31%) and 20 were males (69%) while among the 23 patients diagnosed with atypical Parkinsonian Disorders, 9 patients (39%) were females and 14 were males (61%). Thus, the two groups were comparable and the results on this parameter were statistically **not significant** (*p* value=0.542) {Figure 3}.

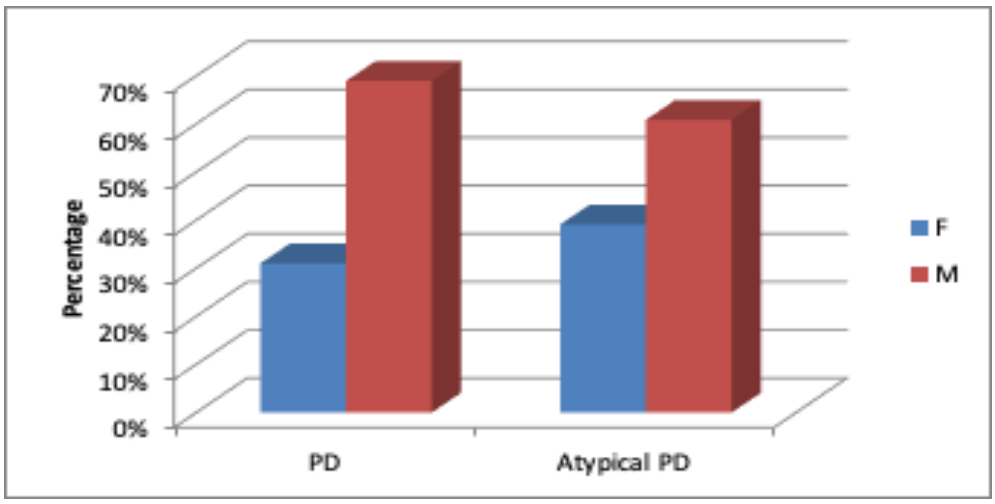

Figure 3: Gender Distribution in the total cohort

SLEEP-RELATED SYMPTOMS:

Among the 52 patients who were studied and analysed, 7 patients (14%) had no sleep-related complaints while 45 patients (86%) were suffering from sleep-related complaints. All these 7 patients with no sleep-related complaints belonged to PD group, while all the 23 patients who had been diagnosed with atypical Parkinsonian Disorders had sleep-related complaints {Table 2, Figure 4}.

Amongst those who had sleep-related complaints (n=45), the most common complaint was *insomnia*, which was present in 25 patients (48%). Insomnia was present in 8 of the 29 PD patients (28%) while in atypical Parkinsonian Disorders, it was seen in 17 of the 23 patients (74%); which was statistically **significant** (*p* value=0.001). Thus, the two groups varied significantly regarding this complaint {Table 2, Figure 4}.

Excessive Daytime sleepiness was the next common complaint, in 19 patients of the total cohort (37%). It was present in 7 of the 29 PD patients (24%) and in atypical Parkinsonian Disorders, it was seen in 12 of the 23 patients (52%); {Figure 4} which was statistically **significant** (*p* value=0.037).

This was followed by *Early Waking,* present in in 10 of the 52 patients studied (19%). It was seen in 7 of the 29 PD patients (24%) and in 3 of the 23 patients (13%) of the atypical Parkinsonian Disorders patients; which was statistically **not significant** (*p* value=0.313).

The next two common complaints were *Mood Disturbance* and *Breathing Difficulty at night*, which were present in 9 patients each (17%). For *Mood Disturbance,* the division was 8 of the 29 PD patients (28%) and in only 1 of the 23 atypical Parkinsonian Disorders patients (4%); which was statistically **significant** (*p* value=0.028).

However, for *Breathing Difficulty at night* the division was 4 of the 29 PD patients (14%) and in 5 of the 23 atypical Parkinsonian Disorders patients (22%); which was statistically **not significant** (*p* value=0.452).

The next common chief sleep related complaint was *Nocturia,* which was observed in 8 of the 52 total patients (15%). This was absent in PD patients but observed in 8 of the 23 atypical Parkinsonian Disorders patients (35%); which was statistically **significant** (*p* value=0.001) {Table 2}.

The next complaint noted was *Irresistible Urge to Move Legs* which was seen in 7 patients (13%). This were not seen in PD patients and seen in 7 of the 23 atypical Parkinsonian Disorders patients (30%); which was statistically **significant** (*p* value=0.001).

Dream Enacting Behaviour was the next common sleep-related complaint seen in our cohort in 6 of 52 patients (12%), which was in none of the PD patients but seen in 6 of the 23 atypical Parkinsonian Disorders patients (26%); which was statistically **significant** (*p* value=0.003) {Table 2, Figure 4}.

Cramps was the least common sleep-related complaint, noted in 4 of 52 patients (8%), which was distributed as all of them being PD patients(n=4) (14%) but not seen in the atypical Parkinsonian Disorders patients; which was statistically **not significant** (*p* value=0.06) {Table 2, Figure 4}.

Two sleep-related complaints studied, namely, *Sleep Attacks and Sleep Related Injurious Behaviour,* were absent in all the patients studied. Hence, they could not be compared among the 2 groups.

Table 2: Sleep-related Complaints in the study population

Sleep-Related Complaint	Present(Y) Absent (N)	Disorders				Total (n)	*p*-value
		PD	PD	Atypical PD	Atypical PD		
INSOMNIA	N	21	72%	6	26%	27	0.001
	Y	8	28%	17	74%	25	
EARLY WAKING	N	22	76%	20	87%	42	0.313
	Y	7	24%	3	13%	10	
EXCESSIVE DAY TIME SLEEPINESS	N	22	76%	11	48%	33	0.037
	Y	7	24%	12	52%	19	
MOOD DISTURBANCE	N	21	72%	22	96%	43	0.028
	Y	8	28%	1	4%	9	
NOCTURIA	N	29	100%	15	65%	44	0.001
	Y	0	0%	8	35%	8	
CRAMPS	N	25	86%	23	100%	48	0.064
	Y	4	14%	0	0%	4	
DREAM ENACTING BEHAVIOUR	N	29	100%	17	74%	46	0.003
	Y	0	0%	6	26%	6	
IRRESISTIBLE URGE TO MOVE LEGS	N	29	100%	16	70%	45	0.001
	Y	0	0%	7	30%	7	
BREATHING DIFFICULTY AT NIGHT	N	25	86%	18	78%	43	0.452
	Y	4	14%	5	22%	9	
Total		**29**	**100%**	**23**	**100%**	**52**	

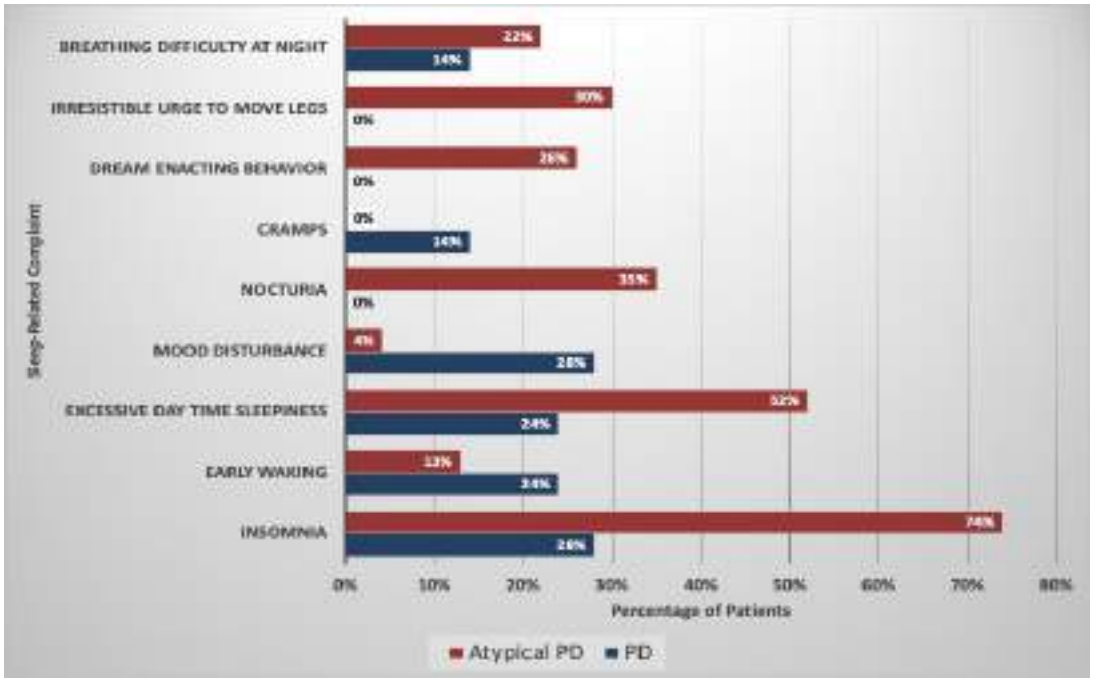

Figure 4: Sleep-related Complaints in the study population (%)

DURATION OF DISEASE

In the 29 patients diagnosed with PD, the mean duration of disease was **2.81** ± 1.38 years (1-7 years), while among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean duration of disease was **2.24 +** 0.45 years (1-3 years). The comparison of disease duration between the two groups was statistically **not significant** (*p* value=0.064) and hence this parameter was comparable between the two groups {Table 3}.

CLINICAL SCORING

For the *Epworth Sleepiness Scale (ESS)*, in the 29 patients diagnosed with PD, the mean score was **8.66** ± 4.34 (2-17) while among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean score was **12.35** ± 3.24 (4-16). The comparison of this scale between the two groups was statistically **significant** (*p* value=0.001) {Table 3}.

Similarly, for the *Parkinson's Disease Sleep Scale-2 (PDSS-2)* in the 29 patients diagnosed with PD the mean score was **13.45** ± 5.80 (3-23) while among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean score was **18.61** ± 3.58 (17-24). The comparison of this scale between the two groups was also statistically **significant** (*p* value=0.0002) {Table 3}.

However, for the *Restless Leg Syndrome rating scale (RLS)*, in the 29 patients diagnosed with PD, the mean score was **3.90** ± 2.50 (0-9) while among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean score was **10.17** ± 7.41 (2-24). The comparison of this scale between the two groups was statistically **significant** as well (*p* value=0.0004) {Table 3}.

Table 3: Age, Duration of Disease and Clinical Scores compared between the 2 groups

PARAMETER	PD		Atypical PD		*p*-value
	Mean	SD	**Mean**	SD	
AGE (years)	**57.24**	11.69	**66.87**	7.50	0.001
DURATION (years)	**2.81**	1.38	**2.24**	0.45	0.064
ESS SCORE	**8.66**	4.34	**12.35**	3.24	0.001
PDSS 2 SCORE	**13.45**	5.80	**18.61**	3.58	0.0002
RLS RATING SCALE	**3.90**	2.50	**10.17**	7.41	0.0004

POLYSOMNOGRAPHY (PSG)

PATIENT POPULATION ON WHICH SLEEP STUDIES WERE PERFORMED

Polysomnography (PSG) was done on 11 of 52 patients (21%). Seven of these 11 patients were males (64%) and 4 patients were females (36%) {Figure 5}.

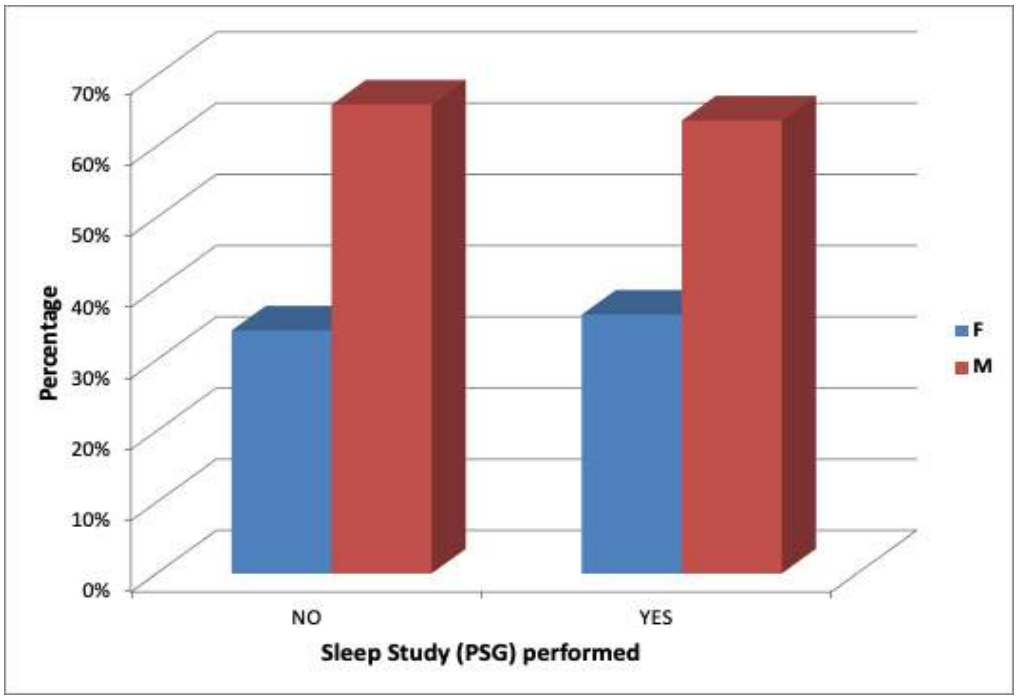

Figure 5: Gender distribution in those whom sleep study was performed (%)

Four out of these 11 had been diagnosed with PD (36%) and 7 out of these 11 patients had been diagnosed with atypical Parkinsonian Disorders (64%). In the 7 patients of atypical Parkinsonian Disorders, the distribution was as follows: PSP- 4 patients, CBGD- 2 patients and 1 patient of MSA.

Mean age in the PD group who underwent PSG was **65.50** ± 7.33 years (59-76 years), while in the patients with Atypical Parkinsonian Disorders who underwent PSG, it was **65.29** ± 5.65 years (57-74 years). Thus, the two groups were comparable with regards to age and this was statistically **not significant** (*p* value=1.00) {Table 4}.

With respect to duration of the disease in these 11 patients, the mean duration of disease was **2.38** ± 0.95 years (1-3 years) in the 4 PD patients, while among the 7 patients diagnosed with atypical Parkinsonian Disorders, the mean duration of disease was **2.07** ± 0.61 years (1-3 years). The comparison of disease duration between the two groups was statistically **not significant** (*p* value=0.326) {Table 4}.

Table 4: Age and Duration of Disease between the 2 groups among those on whom PSG was done

SLEEP STUDY DONE	NO		YES		p-value
	Mean	SD	Mean	SD	
AGE (years)	60.46	11.93	65.36	5.94	0.195
DURATION (years)	2.66	1.17	2.18	0.72	0.207

Table 5: PSG Parameters Assessed

Sleep-Related Complaint	Present(Y) Absent (N)	Sleep Study Done				Total(n)	p-value
		NO	NO%	YES	YES%		
INSOMNIA	N	21	51%	6	55%	27	0.845
	Y	20	49%	5	45%	25	
EARLY WAKING	N	35	85%	7	64%	42	0.104
	Y	6	15%	4	36%	10	
EXCESSIVE DAY TIME SLEEP	N	27	66%	6	55%	33	0.489
	Y	14	34%	5	45%	19	
MOOD DISTURBANCES	N	34	83%	9	82%	43	0.931
	Y	7	17%	2	18%	9	
NOCTURIA	N	37	90%	7	64%	44	0.051
	Y	4	10%	4	36%	8	
CRAMPS	N	38	93%	10	91%	48	0.845
	Y	3	7%	1	9%	4	
DREAM ENACTING BEHAVIOUR	N	37	90%	9	82%	46	0.437
	Y	4	10%	2	18%	6	
IRRESISTIBLE URGE TO MOVE LEGS	N	36	88%	9	82%	45	0.605
	Y	5	12%	2	18%	7	
BREATHING DIFFICULTY AT NIGHT	N	35	85%	8	73%	43	0.325
	Y	6	15%	3	27%	9	
Total		41	100%	11	100%	52	

TOTAL SLEEP TIME (MINUTES)

The mean value of total sleep time in PD patients was noted to be **360** ± 54.80 minutes (282-402 minutes) in the 4 PD patients, while among the 7 patients diagnosed with atypical Parkinsonian Disorders, the mean value of total sleep time was **248.71** ± 77.79 minutes (167-389 minutes), which was statistically **significant** (*p* value=0.023) {Figure 6}.

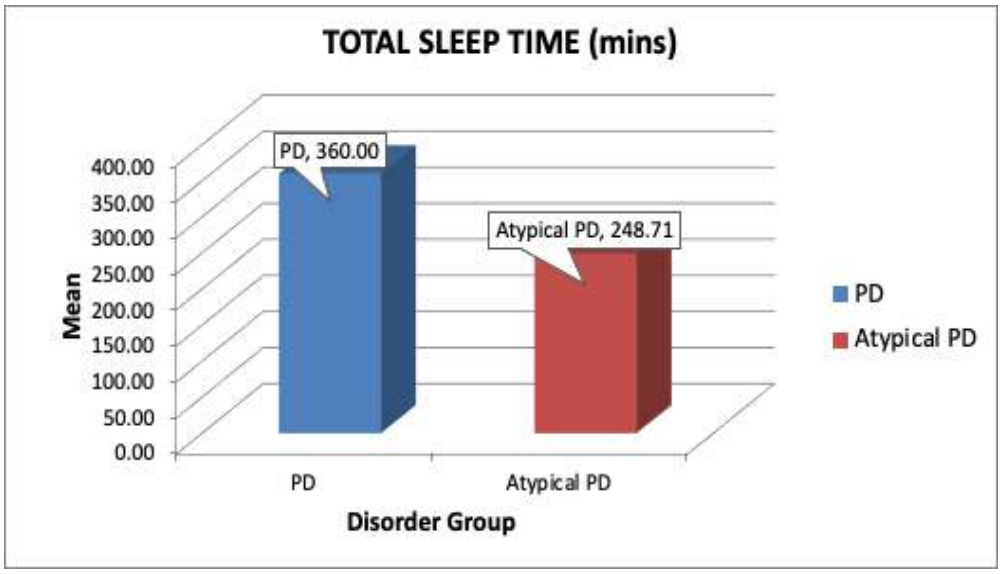

Figure 6: Total Sleep time among whom sleep study was performed (minutes)

SLEEP EFFICIENCY (%)

Among the 7 patients of atypical Parkinsonian Disorders on whom PSG was performed, the mean value of sleep efficiency was **62.64** ± 10.83% (51.63-82.11%), which was **significantly** lower (*p* value=0.023) than the mean value of sleep efficiency in the 4 PD patients on whom PSG was performed, which was noted to be **81.35** ± 3.07% (78.22-84.53%) {Figure 7}.

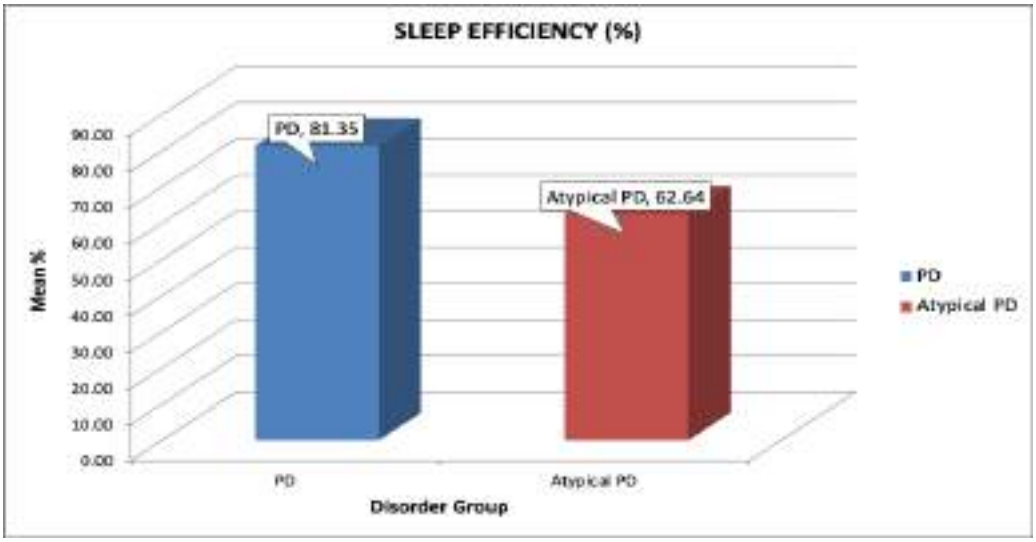

Figure 7: Sleep efficiency among whom sleep study was performed (%)

N1 SLEEP PERCENTAGE (%)

The mean value of N1 sleep percentage in the 4 PD patients on whom PSG was done was noted to be **9.43** ± 6.05 % (5.24-18.42%), while among the 7 patients of atypical Parkinsonian Disorders who underwent PSG, the mean value of N1 sleep percentage was **32.11** ± 22.82% (11.62-77.41%), which was **significantly higher** (*p* value=0.023) {Figure 8}.

N2 SLEEP PERCENTAGE (%)

The mean value of N2 sleep percentage in the 4 PD patients was found as **59.28** ± 4.42 % (54.70-63.41%), while among the 7 patients of atypical Parkinsonian Disorders, the mean value of N2 sleep percentage was **53.63** ± 18.49% (22.62-68.40%), which was **not significant** (*p* value=0.850) {Figure 8}.

N3 SLEEP PERCENTAGE (%)

Similarly, the mean value of N3 sleep percentage in the 4 PD patients was found as **17.03** ± 2.36 % (14.54-20.23%), while among the 7 patients of atypical Parkinsonian Disorders, the mean value of N3 sleep percentage was **10.94** ± 8.96% (0-25.11%), which was again **not significant** (*p* value=0.089) {Figure 8}.

REM SLEEP PERCENTAGE (%)

In 3 out of the 7 patients of atypical Parkinsonian Disorders who underwent PSG, REM sleep was not attained. In the 4 PD patients on whom PSG was done, the mean value of REM sleep percentage was noted to be **14.28** ± 2.73 % (12.41-18.33%), which was **significantly higher** (*p* value=0.008) than the remaining 4 patients of atypical Parkinsonian Disorders who attained REM sleep, in whom the mean value was **3.30** ± 3.41% (0-8.10%) {Figure 8}.

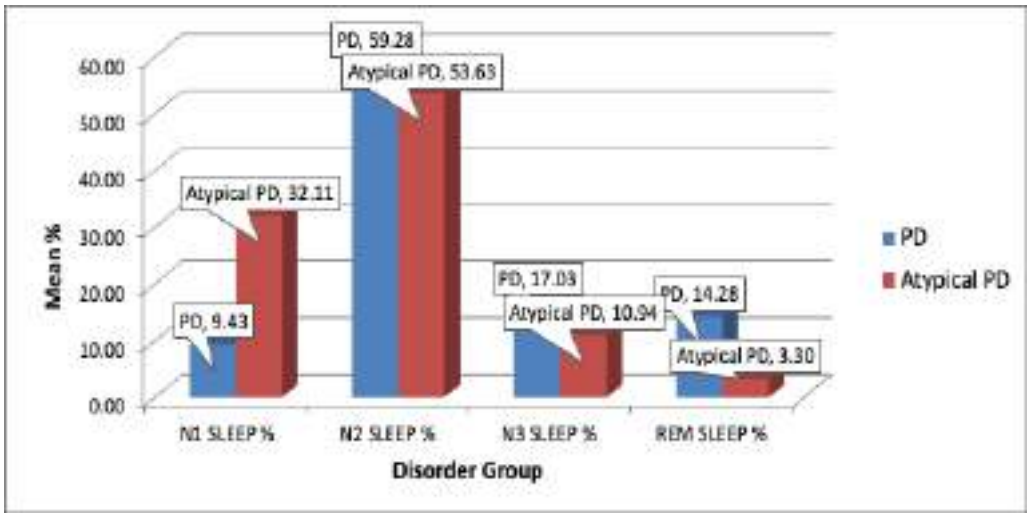

Figure 8: Sleep percentages (N1, N2, N3 and REM) in the study groups

SLEEP LATENCY (MINUTES)

The mean value of sleep latency in the 4 PD patients was noted to be **13.75** ± 3.95 minutes (9.20-17.31 minutes) as compared to the 7 patients diagnosed with atypical Parkinsonian Disorders in whom the mean value of sleep latency was **19.71** ± 16.50 minutes (4.00-55.52 minutes), which was statistically **not significant** (*p* value=0.507) {Figure 9}.

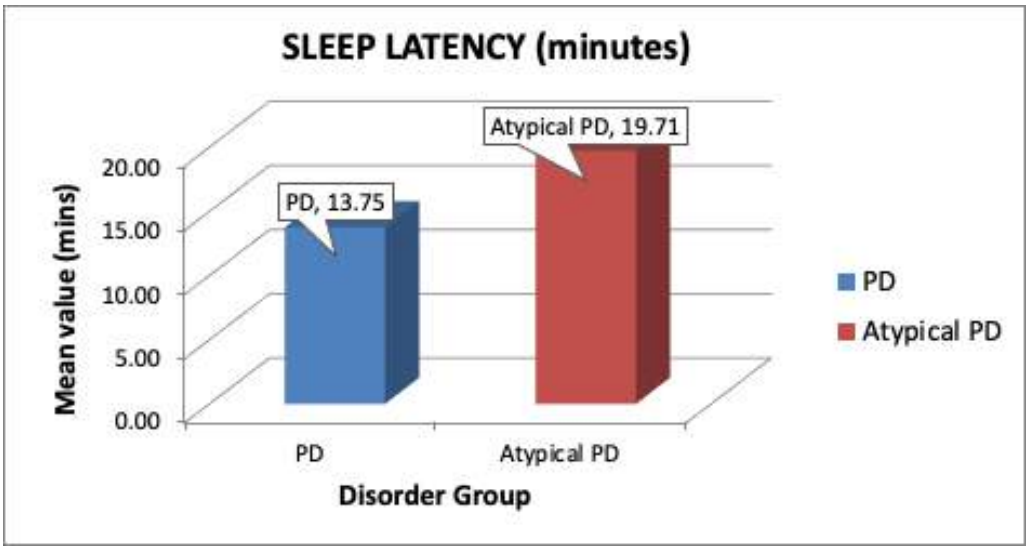

Figure 9: Sleep Latency (minutes) in the study groups

REM LATENCY (MINUTES)

In the 4 PD patients on whom PSG was performed, the mean value of REM latency was noted to be **99.33** ± 7.32 minutes (92.64-106.11 minutes) as compared to the 4 patients diagnosed with atypical Parkinsonian Disorders who attained REM sleep on PSG in whom the mean value of REM latency was **115.93** ± 12.54 minutes (104.00-128.72 minutes), which was statistically **not significant** (*p* value=0.083) {Figure 10}.

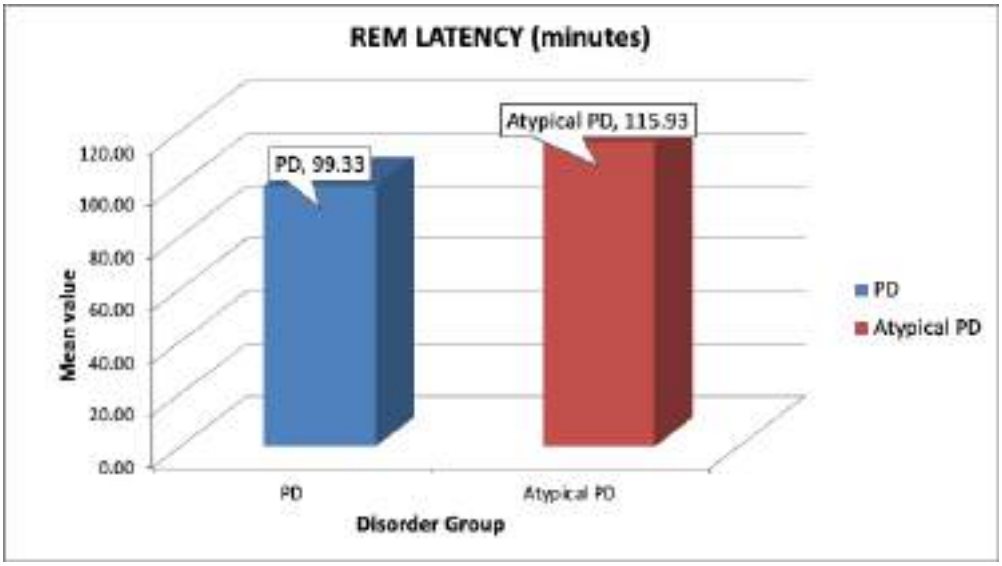

Figure 10: REM sleep Latency (minutes) in the study groups

APNOEA- HYPOPNEA INDEX (AHI)

Out the 4 PD patients on whom PSG was done, the mean value of AHI was noted to be **10.91** ± 5.86 (4.83-18.76) as compared to the 7 patients diagnosed with atypical Parkinsonian Disorders who underwent PSG in whom the mean value of AHI was **8.12** ± 9.04(1.38-27.44), which was statistically **not significant** (*p* value=0.257) {Figure 11}.

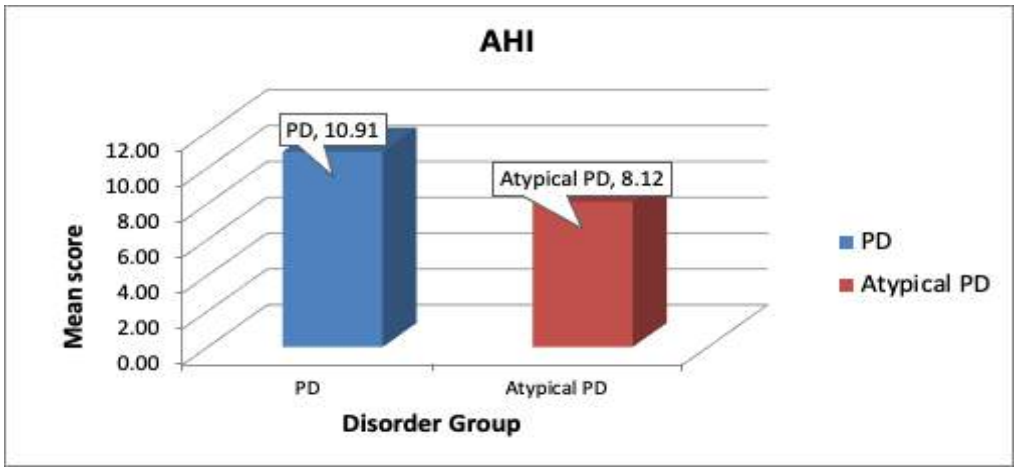

Figure 11: AHI score in the study groups

PERIODIC LEG MOVEMENT INDEX (PLMI)

The 4 PD patients who underwent PSG attained a mean value of PLMI as **5.57** ± 1.07 (5.04-7.15) whereas the 7 patients of atypical Parkinsonian Disorders who underwent PSG had a mean value of PLMI as **29.24** ± 50.61(3.23-142.21), which was statistically **not significant** (*p* value=0.345) {Figure 12}.

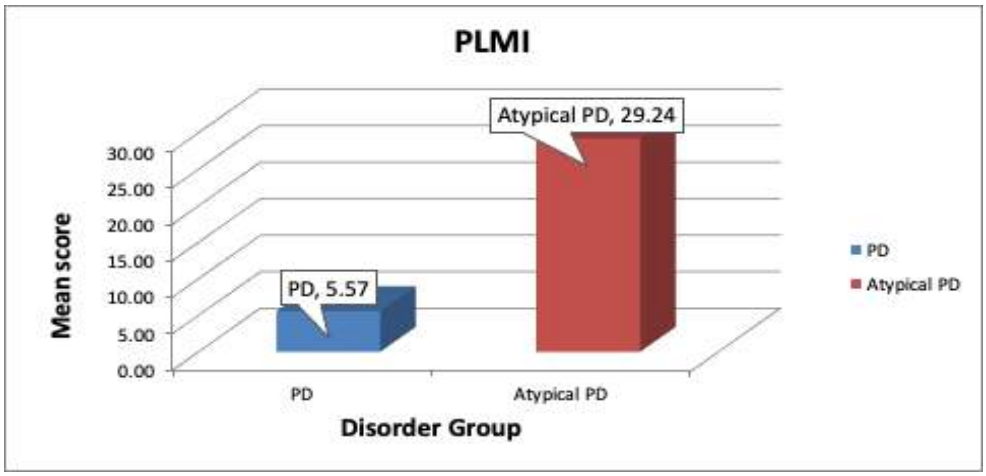

Figure 12: PLMI score in the study groups

AVERAGE ARTERIAL OXYGEN SATURATION (avg. SaO_2) (%)

The mean value of avg. SaO_2 was noted to be **94.00** ± 2.16 % (92.00-97.00%) in the 4 PD patients on whom PSG was done, which was statistically **not significant** (*p* value=0.008) compared to the mean value was **95.43** ± 1.99% (92.00-98.00%) in the 7 patients of atypical Parkinsonian Disorders {Figure 13}.

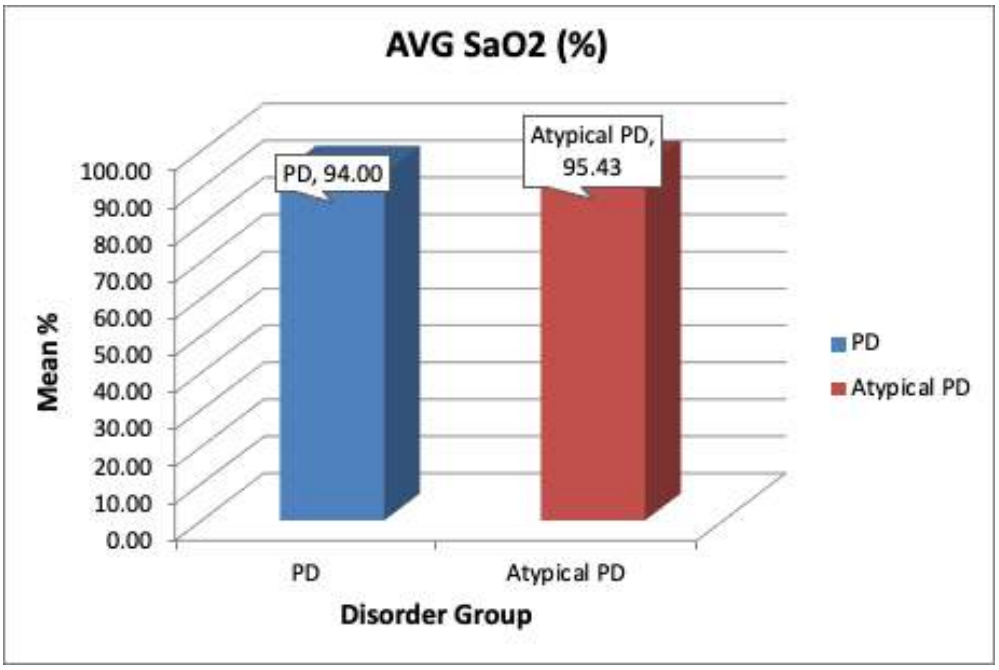

Figure 13: Avg. SaO_2 in the study groups

MINIMUM ARTERIAL OXYGEN SATURATION (min. SaO_2) (%)

The mean value of min. SaO_2 was found to be **85.50** ± 5.92 % (80.00-92.00%) in the 4 PD patients which was statistically **not significant** (*p* value=0.255) compared to the mean value was **89.57** ± 3.31% (84.00-94.00%) in the 7 patients of atypical Parkinsonian Disorders {Figure 14}.

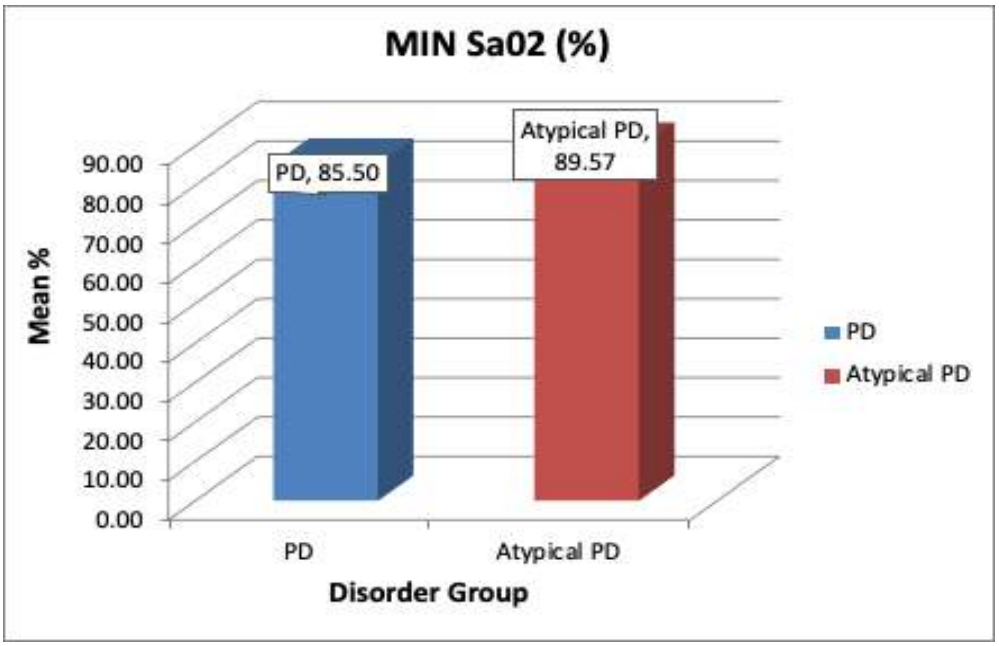

Figure 14: Min. SaO_2 in the study groups

SPECTRUM OF ATYPICAL PARKINSONIAN DISORDERS

SLEEP RELATED SYMPTOMS

There were 23 patients of atypical Parkinsonian Disorders who fulfilled the inclusion criteria of the study. All 23 of them had sleep-related complaints (100%).

The most common complaint in this group was also *insomnia*, which was present in 17 patients (74%). Across the various types, insomnia was present in 4 of the 5 patients (80%) each of CBGD and those suffering from MSA, 7 of the 9 patients (78%) diagnosed with PSP and 2 of the 4 patients (50%) diagnosed with DLB {Table 6}.

Excessive Daytime sleepiness was the second most common complaint, present in 12 of the 23 patients (52%) of atypical Parkinsonian Disorders. Amongst the types, it was found in all of the 5 patients (100%) suffering from MSA, 2 of the 4 patients (50%) of DLB, followed by 4 of the 9 patients (44%) diagnosed with PSP and only 1 of the 5 patients (20%) of CBGD {Table 6}.

The third most common chief sleep related complaint among the atypical Parkinsonian Disorders patients was *Nocturia,* which was observed in 8 of the 23 patients studied (35%). However, it was seen only in 2 of the 4 diseases studied: observed in 6 of the 9 patients (67%) diagnosed with PSP and noted in 2 of the 5 patients (40%) of CBGD {Table 6}.

The next common complaint noted was *Irresistible Urge to Move Legs,* which was seen in 7 of the 23 atypical Parkinsonian Disorders patients (30%). *Irresistible Urge to Move Legs* was present in three of the diseases studied of this broad group: 4 of the 5 CBGD patients (80%), 2 of the 4 patients (50%) diagnosed with DLB and 1 of the 9 patients (11%) diagnosed with PSP {Table 6}.

Dream Enacting Behaviour was the next common sleep-related complaint was seen in 6 of the 23 atypical Parkinsonian Disorders patients (26%). It was found in three of the diseases: interestingly in 4 of the 4 patients (100%) diagnosed with DLB, 1 of the 5 patients (20%) each of CBGD and MSA.

Breathing Difficulty at night was noted to be the next common sleep related complaint, present in 5 of the 23 atypical Parkinsonian Disorders patients (22%) and very interestingly seen in only MSA patients and that too all 5 of them (100%).

This was followed by *Early Waking* in 3 of the 23 patients (13%) of the atypical Parkinsonian Disorders patients noted exclusively in PSP patients, 3 out of 9 patients (33%).

The next common complaint was *Mood Disturbance* seen in only 1 of the 23 atypical Parkinsonian Disorders patients (4%), again only in a PSP patient, 1 out of 9 patients (11%) {Table 6}.

Three sleep-related complaints studied, namely, *Cramps, Sleep Attacks and Sleep Related Injurious Behaviour,* were absent in all the atypical Parkinsonian Disorders patients studied {Table 6}.

Table 6: Sleep-related Complaints amongst atypical Parkinsonian Disorders

Sleep-Related Complaint	Present(Y) Absent (N)	Diagnosis Group				Total(n)
		PSP	CBGD	DLB	MSA	
INSOMNIA	N	2	1	2	1	6
	Y	7	4	2	4	17
EARLY WAKING	N	6	5	4	5	20
	Y	3	0	0	0	3
EXCESSIVE DAY TIME SLEEP	N	5	4	2	0	11
	Y	4	1	2	5	12
MOOD DISTURBANCES	N	8	5	4	5	22
	Y	1	0	0	0	1
NOCTURIA	N	3	3	4	5	15
	Y	6	2	0	0	8
CRAMPS	N	9	5	4	5	23
	Y	0	0	0	0	0
SLEEP ATTACKS	N	9	5	4	5	23
SLP RELATED INJURY BEHAVIOUR	N	9	5	4	5	23
DREAM ENACTING BEHAVIOUR	N	9	4	0	4	17
	Y	0	1	4	1	6
IRRESISTIBLE URGE TO MOVE LEGS	N	8	1	2	5	16
	Y	1	4	2	0	7
BREATHING DIFFICULTY AT NIGHT	N	9	5	4	0	18
	Y	0	0	0	5	5
Total		9	5	4	5	23

CLINICAL SCORING

For the *Epworth Sleepiness Scale (ESS)*, in the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean score was **12.35** ± 3.24 (4-16). The ESS score noted among the various diseases was highest in MSA patients, wherein the mean score was **15.00** ± 1.73 (12-16), closely followed by DLB patients where the mean score was **13.50** ± 1.00 (13-15); followed by the CBGD patients in whom the mean score was **12.40** ± 1.82 (10-15) and lastly the PSP patients in whom the mean score was **10.33** ± 3.97 (4-16) {Figure 15}.

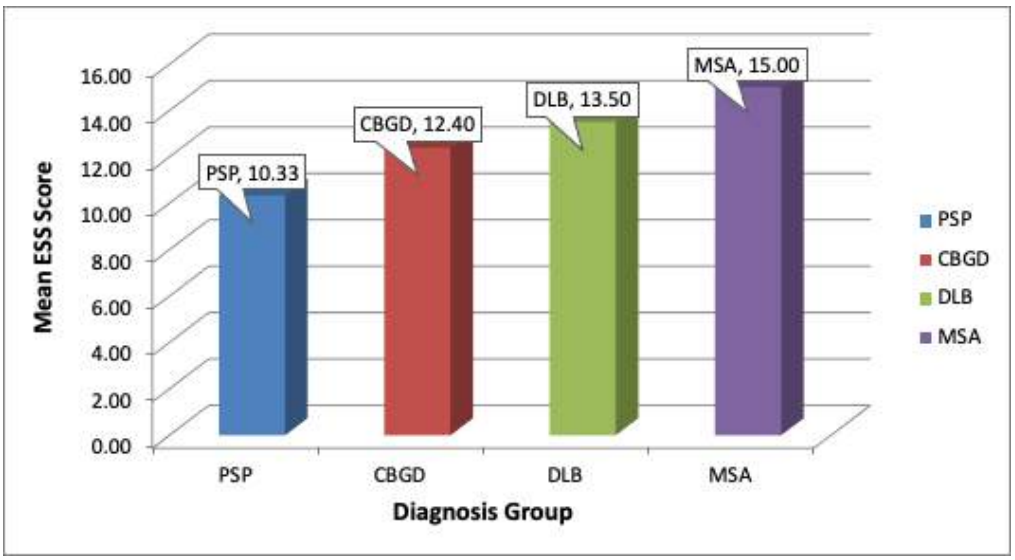

Figure 15: ESS Scoring amongst atypical Parkinsonian Disorders

Similarly, for the *Parkinson's Disease Sleep Scale-2 (PDSS-2)* in patients diagnosed with atypical Parkinsonian Disorders, the mean score was **18.61** ± 3.58 (17-24). The PDSS-2 score observed across this disease spectrum was highest in CBGD patients, in whom the mean score was **20.40** ± 2.30 (18-24), very closely followed by DLB patients wherein the mean score was **20.25** ± 1.26 (19-22); followed by the MSA patients in whom the mean score was **19.40** ± 3.29 (14-22) and the least score was again noted in the PSP patients in whom the mean score was **16.44** ± 4.19 (10-24) {Figure 16}.

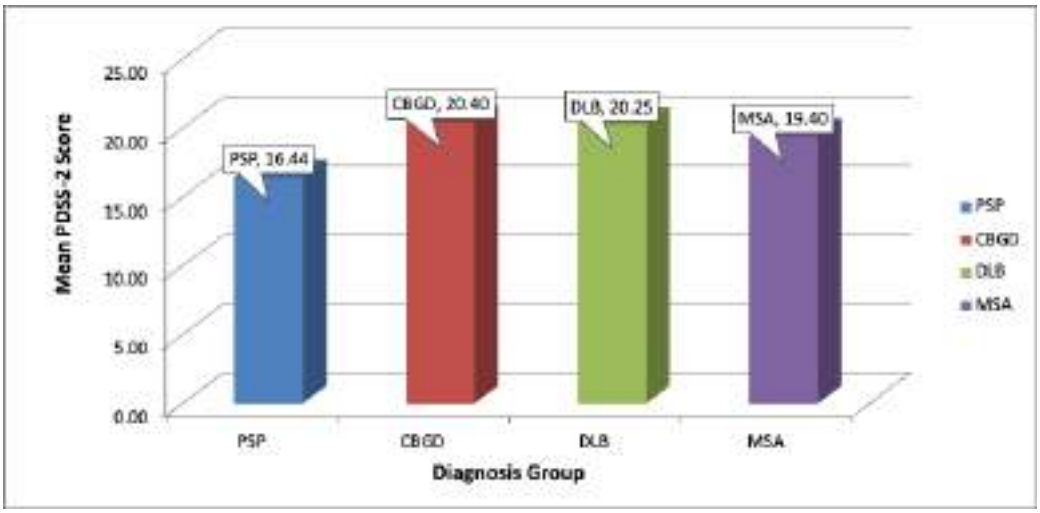

Figure 16: PDSS-2 Scoring amongst atypical Parkinsonian Disorders

However, for the *Restless Leg Syndrome rating scale (RLS)*, in the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean score was **10.17** ± 7.41 (2-24). The RLS scores noted across the 4 diseases constituting this group were as follows: it was found to be highest in CBGD patients, in whom the mean score was **16.40** ± 6.58 (5-22), next in DLB patients wherein the mean score was **15.50** ± 7.33 (8-24); succeeded by the PSP patients in whom the mean score was **6.78** ± 6.67 (2-23) followed by the least score was noted in the MSA patients in whom the mean score was **5.80** ± 1.64 (3-7) {Figure 17}.

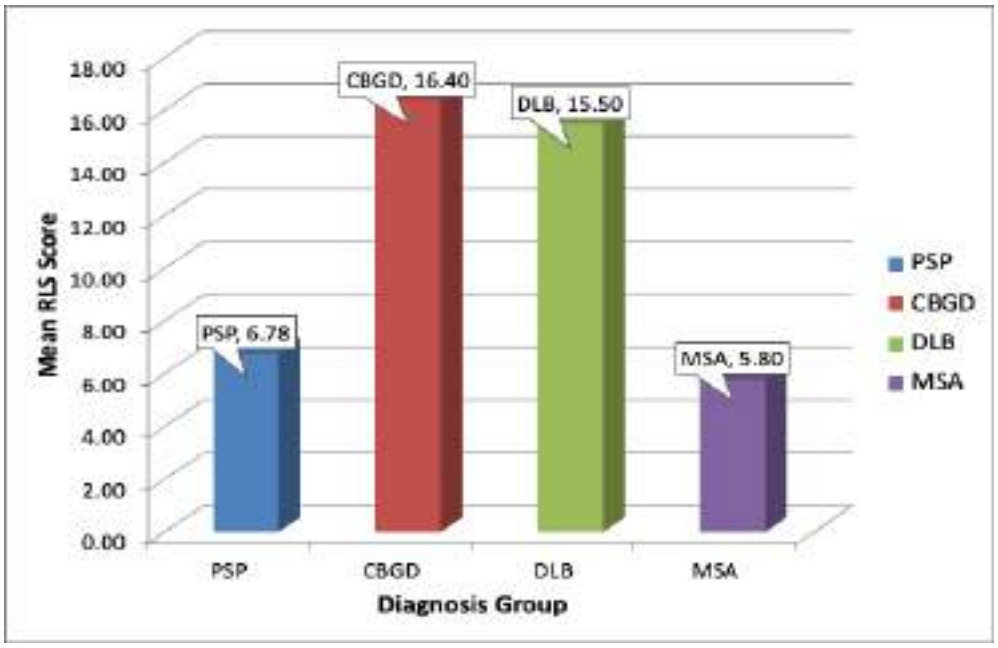

Figure 17: RLS Scoring amongst atypical Parkinsonian Disorders

POLYSOMNOGRAPHY

PATIENT POPULATION ON WHICH SLEEP STUDIES WERE PERFORMED

Out of 23 patients, 7 out of these 11 patients had been diagnosed with atypical Parkinsonian Disorders. In the 7 patients of atypical Parkinsonian Disorders, there were 4 patients of PSP (57%), 2 patients of CBGD (29%) and only 1 patient had MSA (14%).

In the 7 patients with atypical Parkinsonian Disorders who underwent PSG, mean age was **65.29** ± 5.65 years (57-74 years). For the 4 patients of PSP, the mean age was **67.00** ± 5.10 years (62-74 years); for the 2 patients of CBGD, the mean age was **59.50** ± 3.54 years (57-62 years) while for the single patient of MSA, the mean age was **70.00** years {Table 6}.

With respect to duration of the disease, the 7 patients diagnosed with atypical Parkinsonian Disorders, the mean duration of disease was **2.07** ± 0.61 years (1-3 years). For the 4 patients of PSP, the mean age was **2.13** ± 0.85 years (1-3 years); for both the patients of CBGD and the single patient of MSA, the mean age was **2.00** years {Table 7}.

Table 7: Age and Duration of Disease amongst atypical Parkinsonian Disorders on whom Sleep Study was performed

	Diagnosis	n	Mean	Standard Deviation	Minimum	Maximum
AGE (years)	PSP	4	67.00	5.10	62.00	74.00
	CBGD	2	59.50	3.54	57.00	62.00
	MSA	1	70.00		70.00	70.00
	Total	7	65.29	5.65	57.00	74.00
DURATION (years)	PSP	4	2.13	0.85	1.00	3.00
	CBGD	2	2.00	0.00	2.00	2.00
	MSA	1	2.00		2.00	2.00
	Total	7	2.07	0.61	1.00	3.00

PSG PARAMETERS FOR PATIENTS WITH ATYPICAL PARKINSONIAN DISORDERS

TOTAL SLEEP TIME (MINUTES)

The mean value of total sleep time in the 7 patients diagnosed with atypical Parkinsonian Disorders was noted to be **248.71** ± 77.79 minutes (167.00-389.00 minutes). It was found to be longest in PSP patients, in whom the mean value was **274.50** ± 88.58 minutes (173.50-389.00 minutes), next in CBGD patients wherein the mean value was **222.50** ± 78.49 minutes (167.00-278.00 minutes); succeeded by the MSA patient in whom the mean value was **198.00** minutes {Figure 18}.

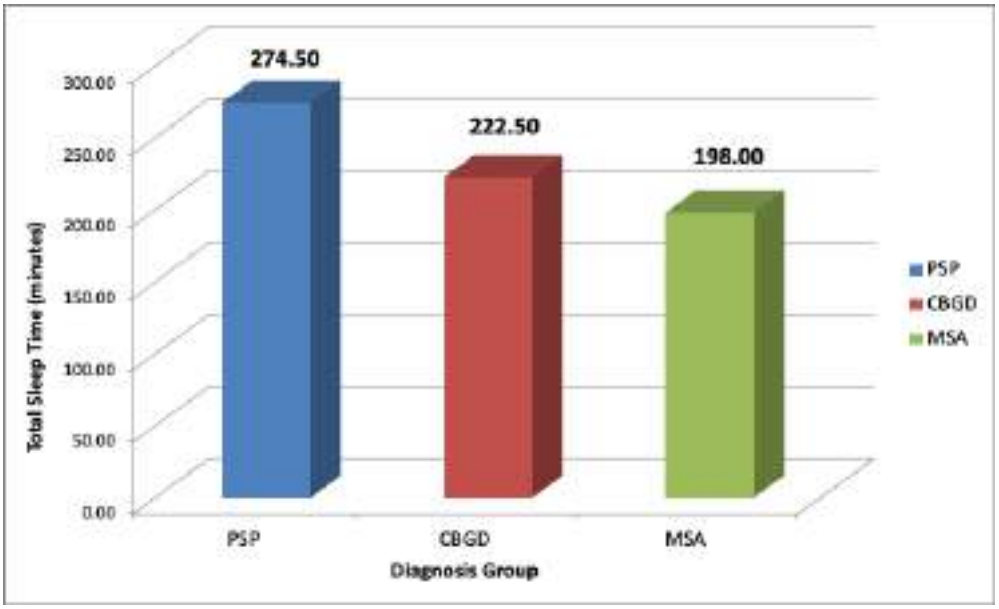

Figure 18: Total Sleep time amongst atypical Parkinsonian Disorders on whom sleep study was performed (minutes)

SLEEP EFFICIENCY (%)

Among the 7 patients of atypical Parkinsonian Disorders on whom PSG was performed, the mean value of sleep efficiency was **62.64** ± 10.83% (51.63-82.11%). It was found to be highest again in PSP patients, in whom the mean value was **66.10** ± 12.51% (51.60-82.10%), next in CBGD patients wherein the mean value was **59.45** ± 10.45% (52.00-66.90%); and lowest again in the MSA patient in whom the mean value was **55.20**% {Figure 19}.

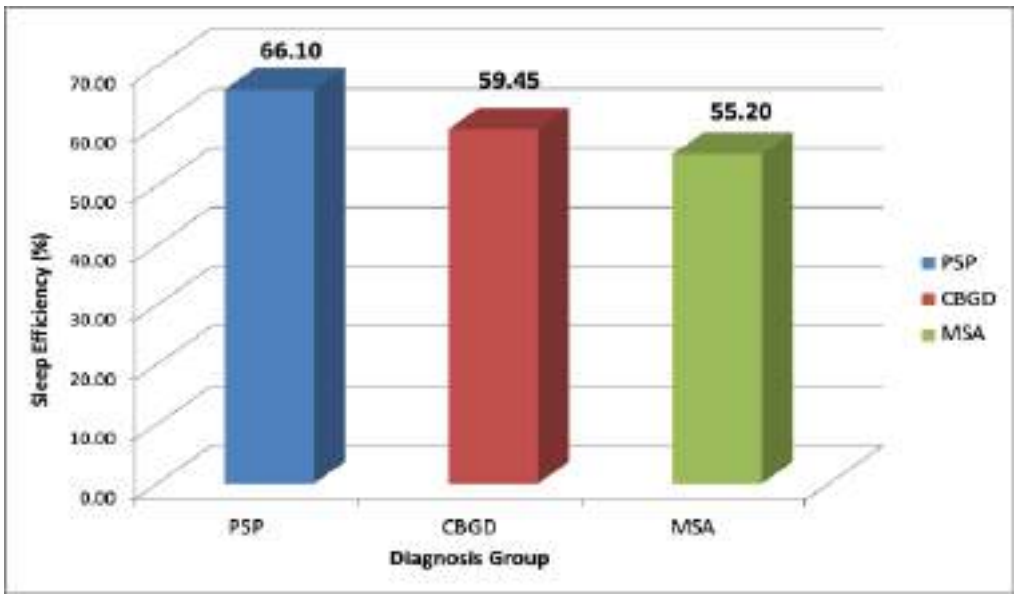

Figure 19: Sleep efficiency amongst atypical Parkinsonian Disorders on whom sleep study was performed

N1 SLEEP PERCENTAGE (%)

The mean value of N1 sleep percentage in the 7 patients of atypical Parkinsonian Disorders who underwent PSG was **32.11** ± 22.82% (11.62-77.41%). It was yet again highest in PSP patients, in whom the mean value was **34.48** ± 30.40% (11.60-77.40%), closely followed by CBGD patients in whom the mean value was **32.85** ± 14.50% (22.60-43.10%); and least in the MSA patient in whom the mean value was **21.20**% {Figure 20}.

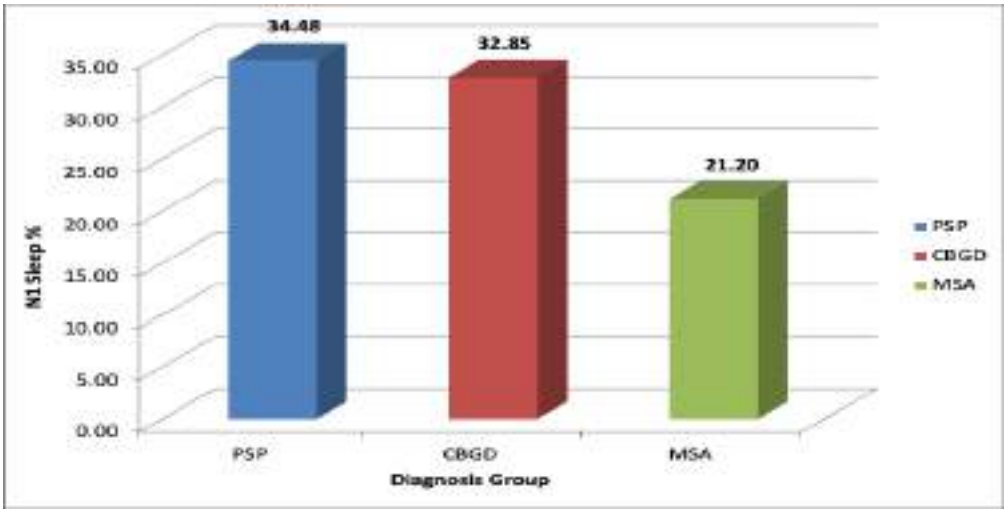

Figure 20: N1 Sleep percentage amongst atypical Parkinsonian Disorders on whom sleep study was performed

N2 SLEEP PERCENTAGE (%)

The mean value of N2 sleep percentage in the 7 patients of atypical Parkinsonian Disorders was observed to be **53.63** ± 18.49% (22.62-68.40%). It was distributed as follows: highest in the MSA patient in whom the mean value was **61.20**%, succeeded by the PSP patients, in whom the mean value was **53.53** ± 20.77% (22.60-67.20%) and lowest in the CBGD patients in whom the mean value was **50.05** ± 25.95% (31.70-68.40%) {Figure 21}.

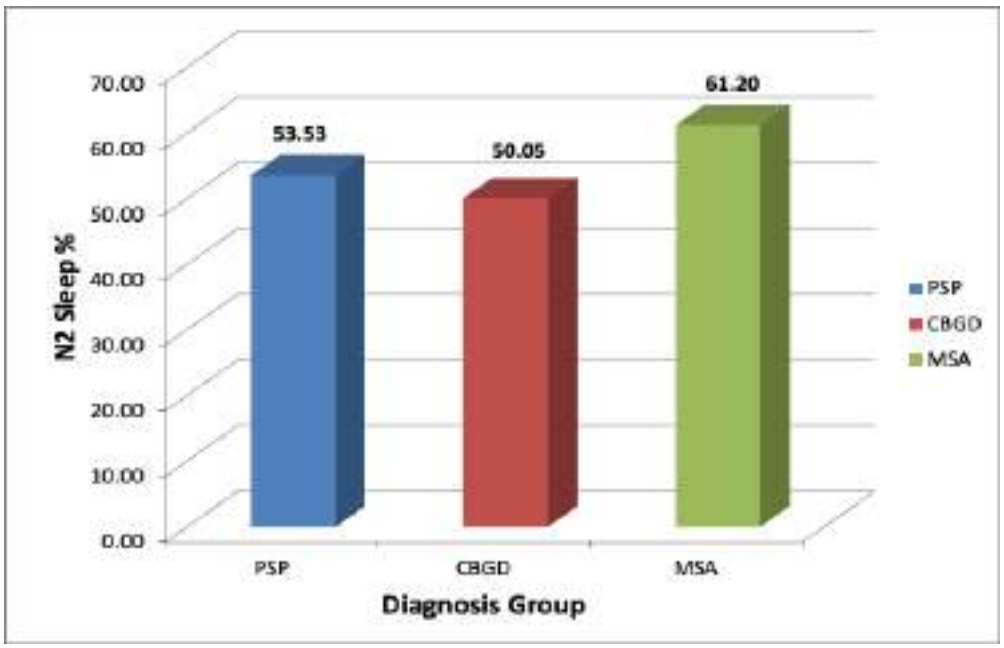

Figure 21: N2 Sleep percentage amongst atypical Parkinsonian Disorders on whom sleep study was performed

N3 SLEEP PERCENTAGE (%)

Similarly, the mean value of N3 sleep percentage in the 7 patients of atypical Parkinsonian Disorders was **10.94** ± 8.96% (0-25.11%), which was stratified as: maximum in the CBGD patients in whom the mean value was **14.95** ± 14.35% (4.80-25.10%), followed by the MSA patient in whom the mean value was **13.70**% and minimum in the PSP patients the mean value of whom was noted to be **8.25** ± 8.30% (0.00-16.40%) {Figure 22}.

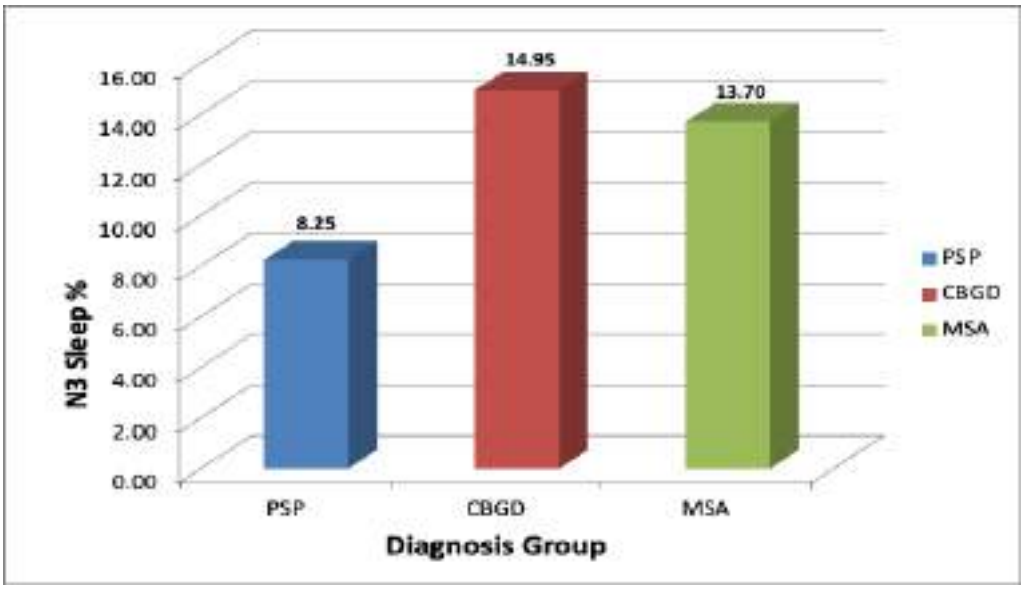

Figure 22: N3 Sleep percentage amongst atypical Parkinsonian Disorders on whom sleep study was performed

REM SLEEP PERCENTAGE (%)

In 3 out of the 7 patients of atypical Parkinsonian Disorders who underwent PSG, REM sleep was not attained. In the remaining 4 patients of atypical Parkinsonian Disorders who attained REM sleep, the mean value was **3.30** ± 3.41% (0-8.10%). This was subdivided to have a mean value of **3.90** in the MSA patient, followed by a mean value of **3.75** ± 4.36% (0-8.10%) in the PSP patients and a mean value of **2.10** ± 2.97% (0-4.20%) in the CBGD patients {Figure 23}.

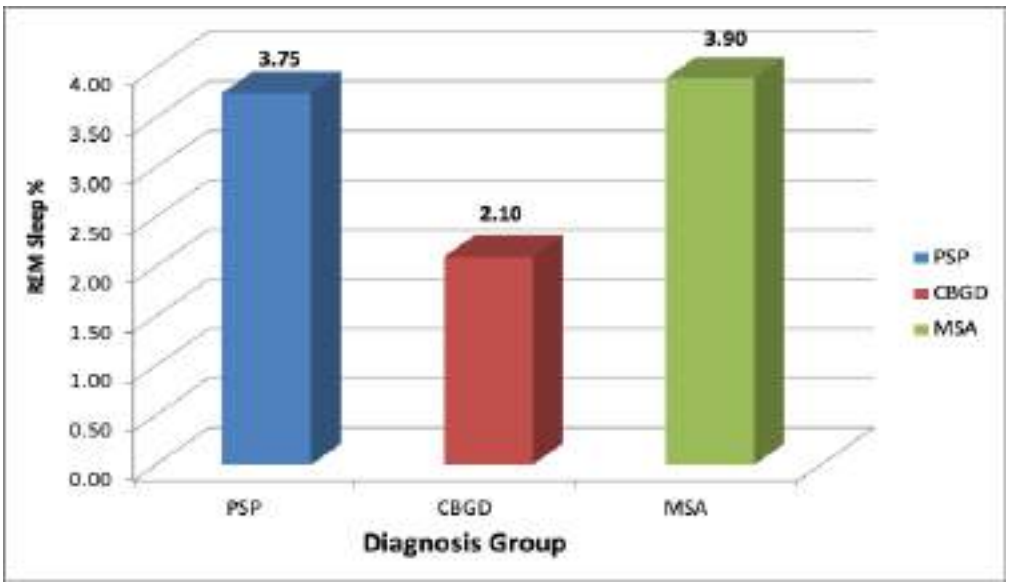

Figure 23: REM Sleep percentage amongst atypical Parkinsonian Disorders on whom sleep study was performed

SLEEP LATENCY (MINUTES)

The mean value of sleep latency in the 7 patients diagnosed with atypical Parkinsonian Disorders was **19.71** ± 16.50 minutes (4.00-55.52 minutes), which was found to be longest in CBGD patients wherein the mean value was **36.95** ± 26.23 minutes (18.40-55.50 minutes), succeeded by PSP patients, in whom the mean value was **12.88** ± 6.15 minutes (4.00-17.30 minutes), and shortest in the MSA patient in whom the mean value was **12.60** minutes {Figure 24}.

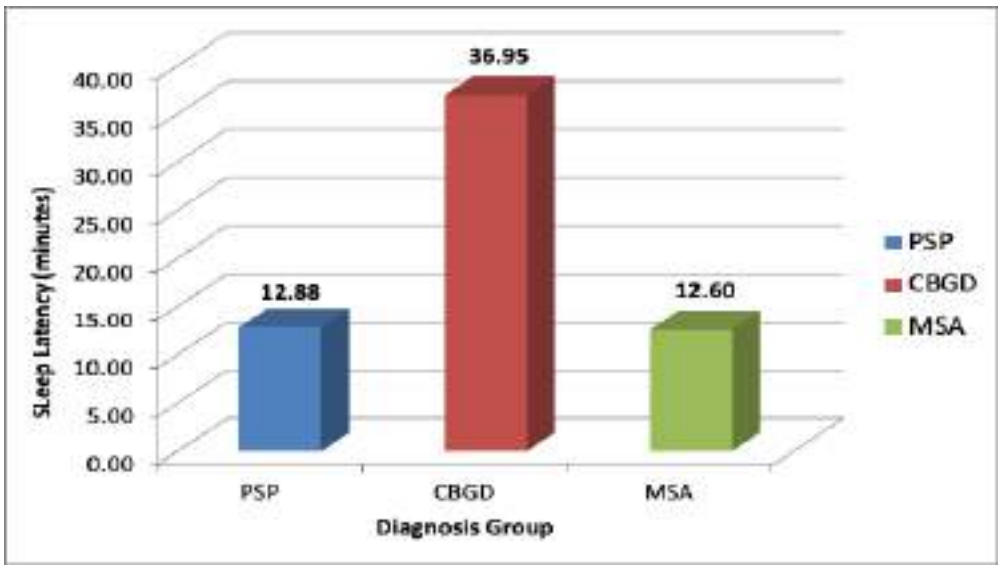

Figure 24: Sleep Latency (minutes) observed amongst atypical Parkinsonian Disorders

REM LATENCY (MINUTES)

In the 4 patients diagnosed with atypical Parkinsonian Disorders who attained REM sleep on PSG, the mean value of REM latency was **115.93** ± 12.54 minutes (104.00-128.72 minutes). Amongst these, maximum latency was observed in the MSA patient, in whom the mean value was **128.70** minutes, closely succeeded by the CBGD patient wherein the mean value was **124.60** minutes; and was minimum in the PSP patients, in whom the mean value was **105.20** ± 1.70 minutes (104.00-106.40 minutes) {Figure 25}.

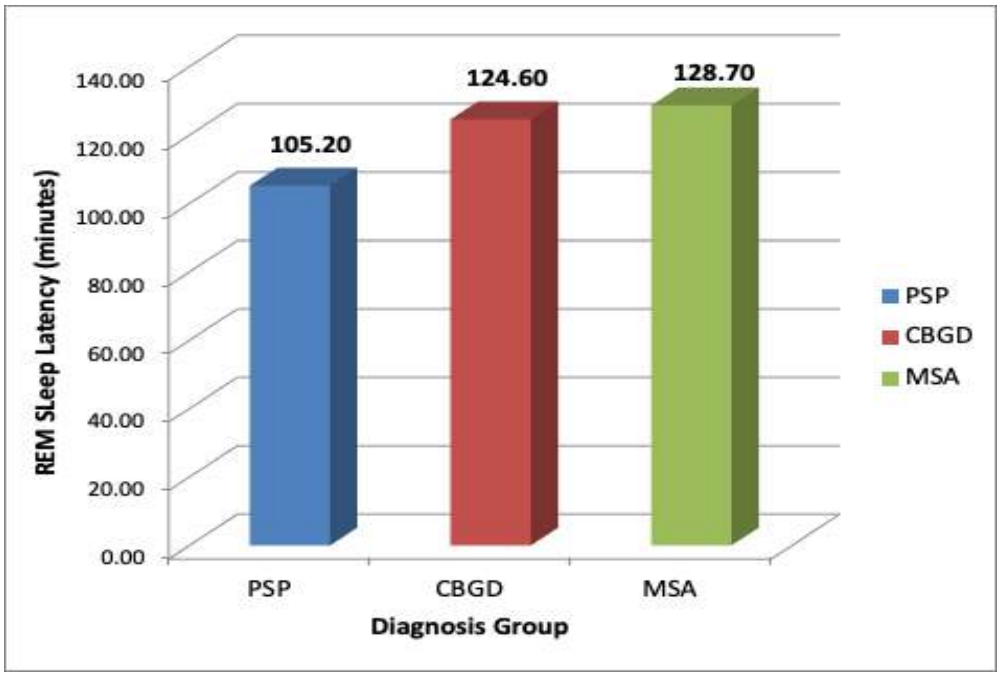

Figure 25: REM Sleep Latency (minutes) observed amongst atypical Parkinsonian Disorders

APNOEA- HYPOPNEA INDEX (AHI)

Out the 7 patients diagnosed with atypical Parkinsonian Disorders who underwent PSG, the mean value of AHI was **8.12** ± 9.04(1.38-27.44) which was obtained as a mean value of **27.44**, the highest, in the MSA patient but substantially lower as mean values of **7.94** ± 2.16 (6.41-9.46) and **3.38** ± 2.75 (1.38-7.21) in the patients diagnosed with CBGD and PSP, respectively {Figure 26}.

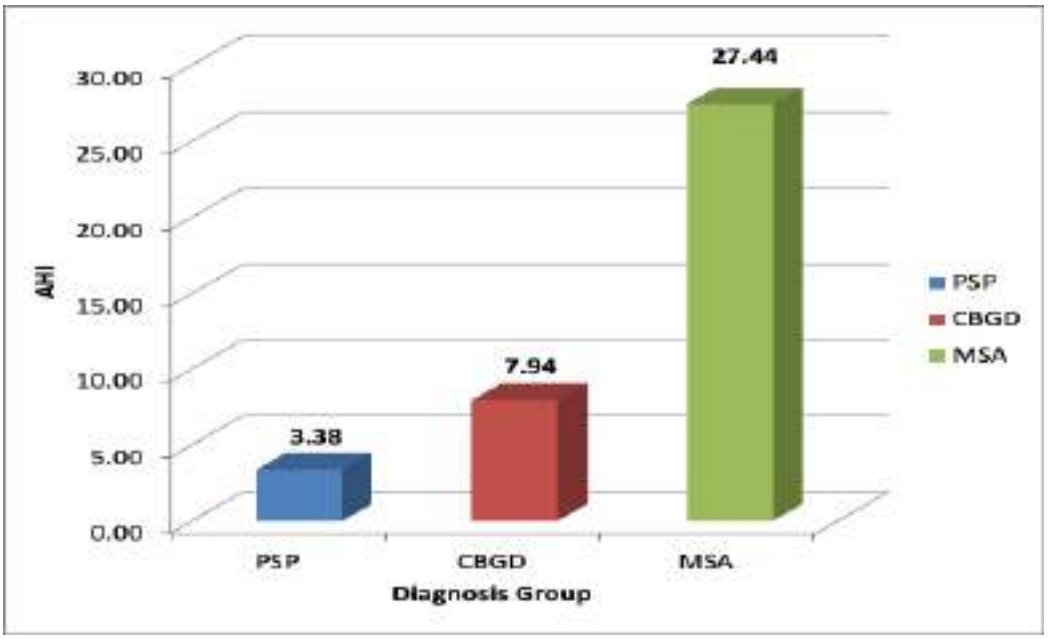

Figure 26: AHI observed amongst atypical Parkinsonian Disorders

PERIODIC LEG MOVEMENT INDEX (PLMI)

The 7 patients of atypical Parkinsonian Disorders who underwent PSG had a mean value of PLMI as **29.24** ± 50.61(3.23-142.21), which was distributed as the highest in the PSP patients with mean value of **41.24** ± 67.37 (4.26-142.21) but substantially lower in the other 2 disease patients, with their mean values as **16.44** ± 18.67 (3.23-29.64) and **6.83** in the CBGD patients and the MSA patient, respectively {Figure 27}.

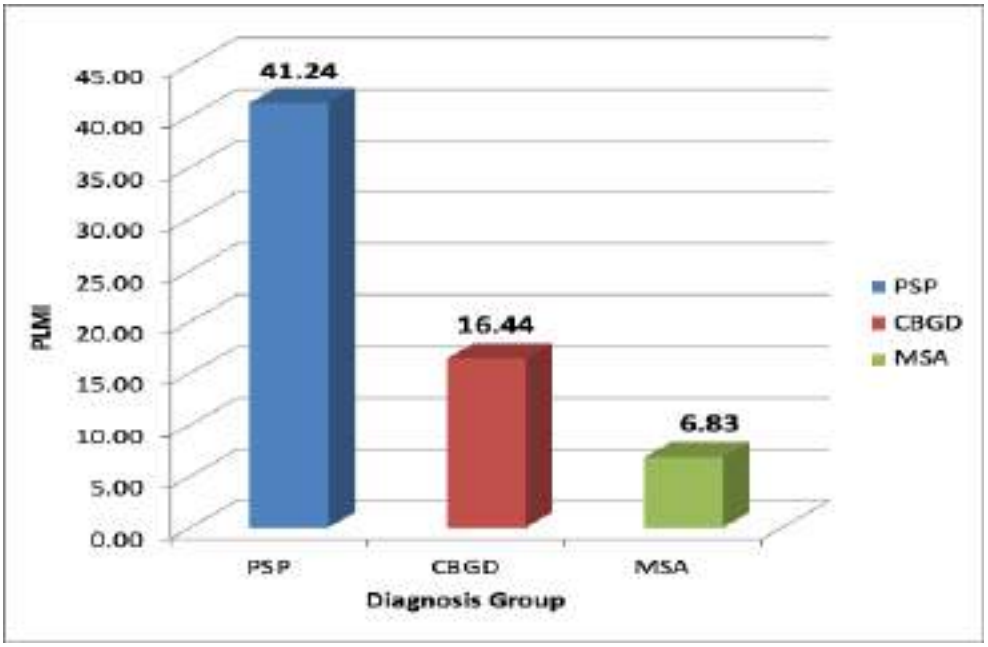

Figure 27: PLMI score observed amongst atypical Parkinsonian Disorders

AVERAGE ARTERIAL OXYGEN SATURATION (avg. SaO_2) (%)

The mean value of avg. SaO_2 was attained as **95.43** ± 1.99% (92.00-98.00%) in the 7 patients of atypical Parkinsonian Disorders. Across the various diseases, the mean was equal in both PSP and CBGD patients at **96.00%**. However, their standard deviations and ranges were different so the avg. SaO_2 was **96.00** ± 1.63% (94.00-98.00%) in the PSP patients and the avg. SaO_2 was **96.00** ± 1.41% (95.00-97.00%) in the CBGD patients, while the avg. SaO_2 was **92.00**% in the MSA patient {Figure 28}.

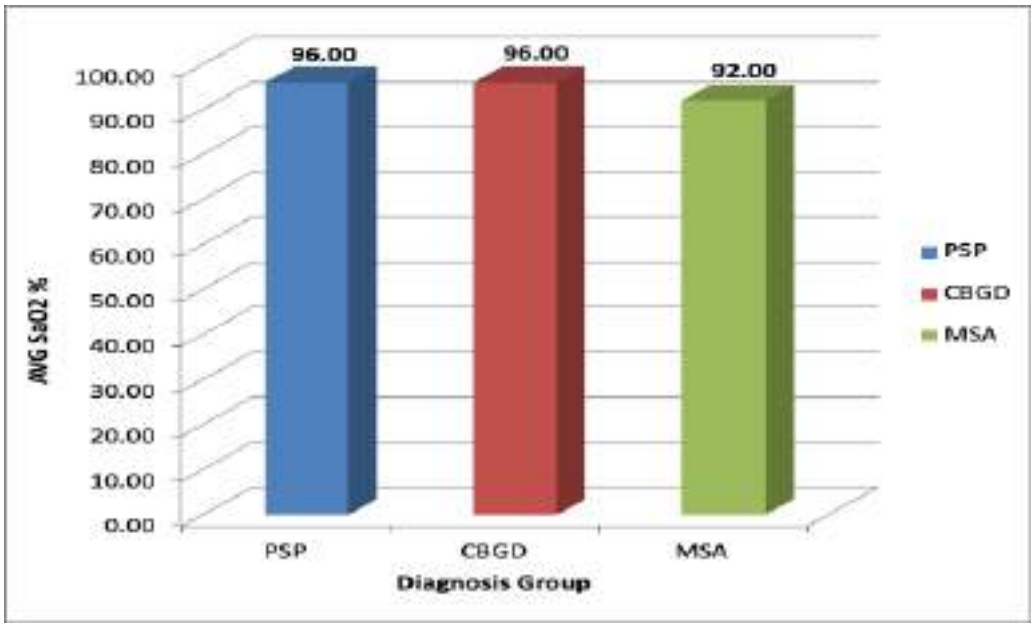

Figure 28: Avg SaO_2 observed amongst atypical Parkinsonian Disorders

MINIMUM ARTERIAL OXYGEN SATURATION (min. SaO_2) (%)

The mean value of min. SaO_2 was found to be **89.57** ± 3.31% (84.00-94.00%) in the 7 patients of atypical Parkinsonian Disorders. This was lowest in the MSA patient, at a value of **84.00**%, while it was considerably maintained in the other 2 disease groups with a mean value of **91.00** ± 2.94% (87.00-94.00%) among the PSP patients and a mean value of **89.50** ± 0.71% (89.00-90.00%) among the CBGD patients {Figure 29}.

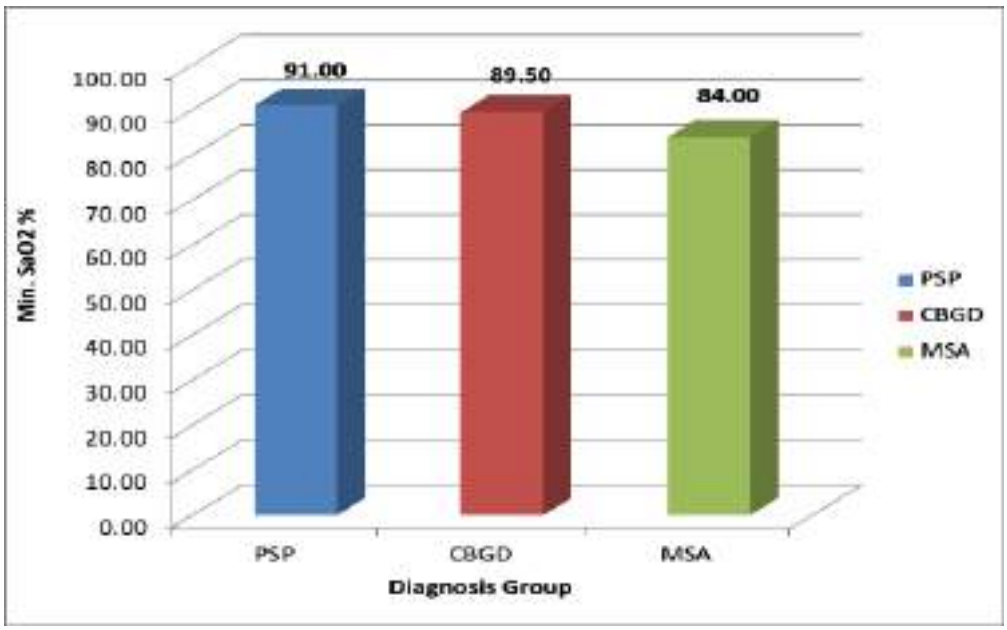

Figure 29: Minimum SaO_2 observed amongst atypical Parkinsonian Disorders

DISCUSSION

Sleep architecture of patients suffering from Parkinson's Disease (PD) although had been studied but in atypical Parkinsonian disorders is poorly determined, even though sleep related complaints are frequently present in both yet underreported. There are few case reports and studies describing the sleep related complaints among the patients of these disorders, although a head-on comparison in between these two groups is lacking in most. Our study aimed to provide type of sleep related problems, questionnaire-based assessment of sleep disturbance and Polysomnography (PSG) study (wherever feasible), in patients of PD and atypical Parkinsonian Disorders. The two Parkinsonism groups were compared with regards their sleep disturbances.

We analysed 52 patients who visited neurology OPD with diagnosis of parkinsonism, with 29 (56%) patients had Parkinson's Disease (PD), while 23 (44%) patients had atypical Parkinsonian Disorders. In a study by *Factor et al, in* 1990 a total of 78 patients of PD were analysed [4]. Similarly, *Gama et al*, in 2010, found and studied 16 patients [48] while *Ramirez et al* in 2015 found 55 patients of PD for sleep-related disturbances [56] respectively.

In this study, among the 23 patients of atypical Parkinsonian Disorders, there were 9 (39%) patients of Progressive Supranuclear Palsy (PSP), 5 (22%) patients of Corticobasal Ganglionic Degeneration (CBGD), 5 (22%) of Multiple System Atrophy (MSA) and 4 (17%) patients of Dementia with Lewy Bodies (DLB). Though in previous studies atypical Parkinsonian Disorders were studied individually such as *Gama et al*, in 2010, studied 13 patients of MSA and 14 patients of PSP along with the PD patients with regard to sleep problems [48]. This study comprehensively studied all categories of atypical Parkinsonian Disorders to actually establish the differences related to sleep problems and polysomnographic parameters among them

The mean age among the PD patients in our study was **57.24**± 11.69 years (32-78 years), while in a study *Factor et al*, 78 patients of

PD were studied with the aim of analysing the frequency of various sleep disorders in Parkinson's Disease, the mean age was **67.6** years[4]. However, in a study by *Gama et al*, in 2010, mean age among the 16 PD patients was **64.0**± 11.20 years [48]. Similarly, *Ramirez et al* in 2015 found a mean **61.9**± 10.9 years in their 55 PD patients [56]. Hence, sleep-related disorders in PD are being earlier diagnosed with advancement in medical science, as the mean age is in decreasing trend from 1990 to 2015. We included patients with disease duration 3 years and hence a lower mean age as compared to previous studies. Our aim was to have a comparable study population and to delineate sleep dysfunctions and PSG parameters that can differentiate early PD from atypical Parkinsonian Disorders, where there is a likelihood of diagnostic dilemma.

Among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean age was **66.87**± 7.50 years (56-87 years) in our study. For the 9 patients of PSP, the mean age was **66.44** ± 6.71 years (56-75 years) in this cohort, while a study by *Gross et al,* in 1978, the age range of PSP patients was 62-67 years [32]. It was also comparable to a study by *Aldrich et al* in 1989 on PSP patients, wherein the mean age was 67 years (60-74 years) [72] and *Montplaisir et al*, conducted in 1997, the mean age was **70.5** ± 6 years [33] and *Sixel-Doring et al* in 2008 found a mean age of **71** ± 8 years [73]. This can also be attributed to a lesser disease duration and hence a lower mean age.

For the 5 patients of CBGD, the mean age was **64.40** ± 7.70 years (57-76 years) in our study population which was in close comparison to the mean age of **64.2** ± 10.1 years (56-78 years) in patients studied by *Roche et al* in 2007 [35]. In our study, for the 5 patients of MSA, the mean age was **65.00** ± 6.40 years (56-72 years) which was similar to the 10 patients of MSA studied by *Stanzani-Maserati et al* in 2014, in which the mean age was **57.8** ± 6.40 years (47-64 years) [17]. However, *Shimohata et al* in 2012 also studied sleep-related disorders among MSA patients and found a mean age to be higher at **62.3** ± 1.7 years (46-78 years) [74] and in a study by *Moreno-Lopez et al,* in 2011 was **62.9** ± 7.9 years (44-82 years) [19], possibly

because of the greater number of MSA patients in these latter 2 studies and their exclusive nature of studying MSA, thereby broadening their age range and increasing the mean.

In a study by *Borroni et al* in 2007 on behavioural and psychological dysfunctions in DLB patients, the mean age was **73.7** ± 7.4 years [15] and a study by *Boddy et al* in 2007, the mean age of DLB patients was **76** ± 7 years [65]. Both of these were quite comparable to the 4 patients of DLB in our cohort, the mean age was **73.25** ± 9.36 years (66-87 years).

In our study, the gender distribution among the 29 patients diagnosed with PD, 9 patients were females (31%) and 20 were males (69%) which was similar to *Ramirez et al* who found a total of 21 female (38%) and 34 males (62%) [56] but incongruent to those of *Factor et al*, in 1990, found a total of 32 females (41%) 46 males (59%)[4] and Gama *et al*, in which the gender distribution among the PD patients was 9 females (56%) 7 males (44%) [48]. However, it was comparable to the 23 patients diagnosed with atypical Parkinsonian Disorders in our study in which 9 patients (39%) were females and 14 were males (61%), making the study population homogenous and easily comparable.

In the 29 patients diagnosed with PD, the mean duration of disease was **2.81** ± 1.38 years (1-7 years), whereas on the other hand *Ramirez et al* in 2015 studied only one group that is PD hence they included all patients which may be a reason for higher mean duration of disease **6.5** ± 6.7 years [56]. Among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean duration of disease was **2.24 +** 0.45 years. Thus, a lower overall duration of disease was observed in our study population.

Among the 52 patients who were studied and analysed in our cohort, 7(14%) patients had no sleep-related complaints while 45 (86%) patients were having sleep-related complaints. This percentage of patients were comparable to the previous study by *Pistacchi et al* which showed range of 40 to 90% while other studies found the sleep-related complaints in 65-95% among PD patients previously reported in

literature [4,3,36]. All the 23 patients who had been diagnosed with atypical Parkinsonian Disorders had sleep-related complaints, the incidence of which cannot be compared as there was no previous study which had studied these disorders as one group.

In our study population, amongst those who had sleep-related complaints (n=45), the most common complaint was *insomnia*, which was present in 25 patients (48%). Insomnia was present in 8 of the 29 PD patients (28%) which was much lower to that of 88% incidence of insomnia among 78 PD patients studied by *Factor et al* [4] and that of 77% of the 400 PD patients studied by *Oerlemans et al* in 2002 [75]. This vast difference could be accounted for by the exclusive nature of including only PD patients in both these studies and a much higher number of patients than our cohort.

In atypical Parkinsonian Disorders, insomnia was seen in 17 (74%) of the 23 patients. Thus, the two groups varied significantly regarding presence of this sleep complaint.

Excessive Daytime sleepiness was the next common complaint noted in 19 (37%) of the included patients. It was present in 7(24%) of the 29 PD patients and this was comparable to other studies showing 15-50% incidence in literature by *Ondo et al* [40] and 29-60% incidence previously reported [18,40,76]. In atypical Parkinsonian Disorders, it was seen in 12 of the 23 patients (52%), which could not be compared from literature due to lack of similar studies.

In order of frequency, *early waking* was noted in 10 (19%) of the 52 patients studied. It was seen in 7(24%) of the 29 PD patients and in 3 (13%) of the 23 patients of the atypical Parkinsonian Disorders patients.

The next two common complaints were *mood disturbance* and *breathing difficulty at night*, which were seen in 9 (17%) patients each. While *mood disturbance* was in 8 (28%) of the 29 PD patients and in only 1 (4%) of the 23 atypical Parkinsonian Disorders patients; *breathing difficulty at night* was noted in 4 of the 29 PD patients (14%) and in 5 of the 23 atypical Parkinsonian Disorders patients (22%).

Nocturia was the other sleep related complaint, which was

observed in 8 of the 52 total patients (15%). This was absent in PD patients but observed predominantly in 8 (35%) of the 23 atypical Parkinsonian Disorders patients.

The next complaint noted was *Irresistible Urge to Move Legs* which was seen in 7 patients (13%). This was not seen in PD patients and this is comparable to that earlier reported, *Wetter et al*, in 2000 of having an incidence up to 15% in PD patients [77]. This complaint was seen in 7 of the 23 atypical Parkinsonian Disorders patients (30%). However, this can be due to shorter mean duration of disease in our study.

Dream Enacting Behaviour was the next common sleep-related complaint seen in our cohort in 6 of 52 patients (12%), which was in none of the PD patients but seen in 6 of the 23 atypical Parkinsonian Disorders patients (26%). This complaint has a low incidence in literature as well, at 15-28% [43,68,78].

Cramps was the least common sleep-related complaint, noted in 4 of 52 patients (8%), which was distributed as all of them being PD patients(n=4) (14%) but not seen in the atypical Parkinsonian Disorders patients. This parameter could not be compared due to lack of similar reporting in other studies.

Two sleep-related complaints studied, namely, *Sleep Attacks and Sleep Related Injurious Behaviour,* were absent in all the patients studied by us. *Sleep Attacks* have a low incidence in other series as well, as low as 0-30%, as reported by *Homann et al* and 0.7%, by *Hobson et al* [76].

CLINICAL SCORING

For the *Epworth Sleepiness Scale (ESS)*, in the 29 patients diagnosed with PD, the mean score was **8.66** ± 4.34 (2-17) which was in close comparison to the mean score of **9.1** ± 6.1 in a study by *Brodsky et al* in 2003 on PD patients [79], as also to the mean score of **7.6** ± 6.1 (0-24) in a study by *Xiang et al* in 2019 on a total of 1221 PD patients [80].

Among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean ESS score was **12.35** ± 3.24 (4-16) which could

not be compared across literature due to lack of studies exploring sleep-related complaints and scores in atypical Parkinsonian Disorders as a whole group.

Similarly, for the *Parkinson's Disease Sleep Scale-2 (PDSS-2)* in the 29 patients diagnosed with PD the mean score was **13.45** ± 5.80 (3-23) which is comparable to that reported in literature by *Trenkwalder et al* in 2011, at **16.5** ± 8.90 (2-40) seen among 113 patients of PD [50]. Among the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean score was **18.61** ± 3.58 (17-24), but this could not be compared with existing literature since this is not a validated tool for the assessment of these disorders.

However, for the *Restless Leg Syndrome rating scale (RLS)*, in the 29 patients diagnosed with PD in our study, the mean score was **3.90** ± 2.50 (0-9) as compared to the much higher mean RLS score of **22.70** ± 10.70 (0-9) found in the 16 PD patients analysed by *You S. et al* in 2019 [81]. In their study, they applied the RLS score only on patients who had symptoms of RLS whereas we had applied the score on all PD patients of our cohort. Among the atypical Parkinsonian Disorders, the mean RLS score was **10.17** ± 7.41 (2-24) which again was scarcely found applied in literature.

In this study, Polysomnography (PSG) was done on 11 of 52 patients (21%). Four out of these 11 had been diagnosed with PD (36%) and 7 out of these 11 patients had been diagnosed with atypical Parkinsonian Disorders (64%). In the 7 patients of atypical Parkinsonian Disorders, the distribution was as follows: PSP- 4 patients, CBGD- 2 patients and 1 patient of MSA.

The mean value of total sleep time in PD patients was noted to be **360** ± 54.80 minutes (282-402 minutes) in our 4 PD patients which was very similar to that observed by Ramirez *et al* in 2015 who found a total sleep time of **345.4** ± 109.40 minutes (292-365 minutes) [56].

The mean value of total sleep time among the 7 patients diagnosed with atypical Parkinsonian Disorders was **248.71** ± 77.79 minutes (167-389 minutes). The mean value of sleep efficiency in these patients was **62.64** ± 10.83% (51.63-82.11%). These parameters could

not be compared to the current literature as there were no studies found which considered PSG in atypical Parkinsonian Disorders as a group.

The mean value of sleep efficiency in the 4 PD patients in our cohort was noted to be **81.35** ± 3.07% (78.22-84.53%), which was quite higher to that observed by *Ramirez et al* in 2015 who found a sleep efficiency of **68.1** ± 18.6% (6-94.3%) [56].

The mean value of N1, N2 and N3 and REM sleep percentages in the 4 PD patients of our cohort was noted to be **9.43** ± 6.05 % (5.24-18.42%), **59.28** ± 4.42 % (54.70-63.41%), **17.03** ± 2.36 % (14.54-20.23%) and **14.28** ± 2.73 % (12.41-18.33%); which was congruent to that noted by *Ramirez et al* who found percentages of **11.9** ± 9.7% (0-47%), **61.2** ± 16.9% (16.8-100%), **13.4** ± 10.2% (0-46.4%) and **13.4** ± 7.6% (0-28.2%) respectively [56]. Among the patients of atypical Parkinsonian Disorders who underwent PSG, the mean value of N1, N2, N3 and REM sleep percentages were **32.11** ± 22.82% (11.62-77.41%), **53.63** ± 18.49% (22.62-68.40%), **10.94** ± 8.96% (0-25.11%) and **3.30** ± 3.41% (0-8.10%). In 3 out of the 7 patients of atypical Parkinsonian Disorders who underwent PSG, REM sleep was not even attained. Thus, our study can help differentiate PD patients from atypical Parkinsonian Disorders using these PSG parameters wherever there is clinical confusion.

The mean value of sleep latency in the 4 PD patients was noted to be **13.75** ± 3.95 minutes (9.20-17.31 minutes) which was quite low as compared to study done by *Ramirez et al,* where the mean value of sleep latency was **29.7** ± 39.6 minutes (1-221.5 minutes) [56], possibly because of higher number of patients and mean duration of disease studied by them, resulting in a much higher range and thus mean. In the 7 patients diagnosed with atypical Parkinsonian Disorders the mean value of sleep latency was **19.71** ± 16.50 minutes (4.00-55.52 minutes).

In the 4 PD patients on whom PSG was performed, the mean value of REM sleep latency was noted to be **99.33** ± 7.32 minutes (92.64-106.11 minutes), which was much lower as compared to

Ramirez et al study where the mean value of REM sleep latency was **187.3** ± 114.3 minutes (0-468.5 minutes) [56].

In the 4 patients diagnosed with atypical Parkinsonian Disorders who attained REM sleep on PSG, the mean value of REM latency was **115.93** ± 12.54 minutes (104.00-128.72 minutes). This again can be used as a distinguishing parameter between these two groups.

The mean value of AHI was **19.9** ± 21.2 (0-75.4) in the study of *Ramirez et al* [56] as compared to the mean value of our 4 PD patients which was **10.91** ± 5.86 (4.83-18.76). In 7 patients of atypical Parkinsonian Disorders who underwent PSG, the mean value of AHI was **8.12** ± 9.04(1.38-27.44).

Ramirez et al found a mean value of PLMI to be **39.4** ± 105.6 (0-540) [56], which was much more compared to **5.57** ± 1.07 (5.04-7.15) of the 4 PD patients of our cohort. Both AHI and PLMI were lower in our study as compared to *Ramirez et al*, affected in all likelihood by the mean duration of disease, which was much more in their patients. In contrast, for the 7 patients of atypical Parkinsonian Disorders who underwent PSG, a mean value of PLMI as **29.24** ± 50.61(3.23-142.21) was obtained.

SLEEP RELATED SYMPTOMS AMONGST ATYPICAL PARKINSONIAN DISORDERS

There were 23 patients of atypical Parkinsonian Disorders who fulfilled the inclusion criteria of the study. All 23 of them had sleep-related complaints (100%), which was in comparison to 70% patients having sleep-related complaints among patients of MSA studied by *Ghorayeb et al* in 2005 [18].

The most common complaint in this group was also *insomnia*, which was present in 17 patients (74%). Across the various types, insomnia was present in 4 of the 5 patients (80%) of CBGD. It was also present in 4 of the 5 MSA patients (80%), which was much higher than 20% among patients of MSA studied by *Ghorayeb et al* in 2005 [18]. Additionally, in our study, 7 of the 9 patients (78%) diagnosed with PSP and 2 of the 4 patients (50%) diagnosed with DLB had insomnia which

was very similar to that reported by *Rongwe et al* in 2010 at 47% among DLB patients [82].

Excessive Daytime sleepiness was the second most common complaint, present in 12 of the 23 patients (52%) of atypical Parkinsonian Disorders. Amongst the types, it was found in all of the 5 patients (100%) suffering from MSA, which was again much higher, double the 50% incidence observed in patients of MSA studied by *Ghorayeb et al* [18]. This symptom was also seen in 2 of the 4 patients (50%) of DLB, followed by 4 of the 9 patients (44%) diagnosed with PSP and only 1 of the 5 patients (20%) of CBGD.

The third most common sleep related complaint among the atypical Parkinsonian Disorders patients was *Nocturia,* which was observed in 8 of the 23 patients studied (35%). However, it was seen only in 2 of the 4 diseases studied, in 6 of the 9 PSP patients (67%) and 2 of the 5 CBGD patients (40%).

The next common complaint was *Irresistible Urge to Move Legs,* which was seen in 7 of the 23 atypical Parkinsonian Disorders patients (30%). *Irresistible Urge to Move Legs* was present in three of the diseases studied of this broad group: 4 of the 5 CBGD patients (80%), 2 of the 4 DLB patients (50%) and in only 1 of the 9 PSP patients (11%).

Dream Enacting Behaviour was the next common sleep-related complaint which was seen in 6 of the 23 atypical Parkinsonian Disorders patients (26%). It was found in three of the diseases: interestingly in all 4 DLB patients (100%) in our study, which was also high at 75% in a study on DLB patients done by *Ferman et al* in 2011[83]. *Dream Enacting Behaviour* was also seen in one of the 5 patients (20%) each of CBGD and MSA. This was similar to incidence of upto 90% of *Dream Enacting Behaviour* in MSA and DLB patients in literature [23,84-88] while a study done by *Cooper et al* in 2009 who reported an incidence of 5% in CBGD (1 out of 10) patients [82].

Breathing difficulty at night was noted to be the next common sleep related complaint, present in 5 of the 23 atypical Parkinsonian Disorders patients (22%) and very interestingly seen in only MSA

patients and that too all 5 of them (100%). This incidence is much higher than 15-37% breathing difficulty reported in earlier studies done on MSA patients [21,23].

This was followed by e*arly waking, seen* in 3 of the 23 patients (13%) of the atypical Parkinsonian Disorders patients noted exclusively in PSP patients, 3 out of 9 patients (33%). Early waking was not seen in any of the other atypical Parkinsonian Disorders patients (including MSA) as compared to 33% MSA patients studied by *Ghorayeb et al* in 2005 [18].

The next common complaint was *mood disturbance* seen in only 1 of the 23 atypical Parkinsonian Disorders patients (4%), again only in 1 out of 9 PSP patients (11%).

Three sleep-related complaints studied, namely, *Cramps, Sleep Attacks and Sleep Related Injurious Behaviour,* were absent in all the atypical Parkinsonian Disorders patients studied.

CLINICAL SCORING

For the *Epworth Sleepiness Scale (ESS)*, in the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean score was **12.35** ± 3.24 (4-16). The ESS score noted among the various diseases was highest in MSA patients, wherein the mean score was **15.00** ± 1.73 (12-16), closely followed by DLB patients where the mean score was **13.50** ± 1.00 (13-15); both of which were much higher than noted by *Bhalsing et al* who found a mean score of **8.3** ± 3.5 among MSA patients and a mean score of **6.8** ± 4.5 among DLB patients [53]. However, the ESS score noted by *Bhalsing et al* among PSP patients was **7.3** ± 3.6 [53] similar to the PSP patients in our study who had a mean score of **10.33** ± 3.97 (4-16). These irregularities could be accounted for the rare incidence of these disorders, particularly DLB.

The mean ESS score of our CBGD patients was **12.40** ± 1.82 (10-15) which was higher as compared to **4.20** (1-10) noted by *Roche et al* in their CBGD patients [35]. Among the PSP patients, the mean score was **10.33** ± 3.97 (4-16) in our study.

Similarly, for the *Parkinson's Disease Sleep Scale-2 (PDSS-2)* in

patients diagnosed with atypical Parkinsonian Disorders, the mean score was **18.61** ± 3.58 (17-24). The PDSS-2 score observed across this disease spectrum was highest in CBGD patients, in whom the mean score was **20.40** ± 2.30 (18-24), very closely followed by DLB patients wherein the mean score was **20.25** ± 1.26 (19-22); followed by the MSA patients in whom the mean score was **19.40** ± 3.29 (14-22) and the least score was again noted in the PSP patients in whom the mean score was **16.44** ± 4.19 (10-24).

However, for the *Restless Leg Syndrome rating scale (RLS)*, in the 23 patients diagnosed with atypical Parkinsonian Disorders, the mean score was **10.17** ± 7.41 (2-24). The RLS scores noted across the 4 diseases constituting this group were as follows: it was found to be highest in CBGD patients, in whom the mean score was **16.40** ± 6.58 (5-22). In DLB patients of our study population, the mean RLS score was **15.50** ± 7.33 (8-24)

In the PSP patients in our study, the mean RLS score was **6.78** ± 6.67 (2-23) whereas in a PSP patient studied by *Bhalsing et al* it was **23** [53]. The least RLS score was noted in the MSA patients in our study in whom it was **5.80** ± 1.64 (3-7) whereas it was reported to be **26** in the MSA patient studied by *Bhalsing et al* [53]. This can be strongly attributed as in the latter study RLS score was analysed only in symptomatic patients with features of RLS while in our cohort we have applied and analysed it in all patients.

POLYSOMNOGRAPHY ON PATIENTS OF ATYPICAL PARKINSONIAN DISORDERS

PATIENT POPULATION ON WHICH SLEEP STUDIES WERE PERFORMED

In the 7 patients of atypical Parkinsonian Disorders, there were 4 patients of PSP (57%), 2 patients of CBGD (29%) and only 1 patient had MSA (14%).

In the 7 patients with atypical Parkinsonian Disorders who

underwent PSG, mean age was **65.29** ± 5.65 years (57-74 years). For the 4 patients of PSP, the mean age was **67.00** ± 5.10 years (62-74 years) which was very similar to the results of *F. Sixel-Doring et al* who found a mean age of **69** ± 5 years (59-77 years) in a study 20 PSP patients [73]. However, for the 2 patients of CBGD, the mean age was **59.50** ± 3.54 years (57-62 years). This was comparable to *Roche et al* where the mean age of CBGD patients *was* **64.2** ± 10.1 years (56-78 years) [35]*.* For the single patient of MSA, the mean age was **70.00** years compared to the mean age of **57.8** ± 6.4 years (47-64 years) observed by the 10 patients of MSA studied by *Stanzani-Maserati et al* in 2014 [70].

With respect to duration of the disease, 7 patients diagnosed with atypical Parkinsonian Disorder had mean disease duration of **2.07** ± 0.61 years (1-3 years). For the 4 patients of PSP, the mean age was **2.13** ± 0.85 years (1-3 years) which was much lower than the PSP cohort of *F. Sixel-Doring et al,* who in 2009, found a mean disease duration of **8** ± 5 years (2-17 years). Both the patients of CBGD and the single patient of MSA, had a mean duration of **2.00** years, which was quite low as compared to CBGD patients in the study by *Roche et al* in which the mean duration was **3.8** ± 1.3 years (2-5 years) [35] and the MSA patients analysed by *Stanzani-Maserati et al* in which the mean duration was **5** ± 4 years (1-12 years) [70].

PSG PARAMETERS FOR PATIENTS WITH ATYPICAL PARKINSONIAN DISORDERS

TOTAL SLEEP TIME (MINUTES)

The mean value of total sleep time in the 7 patients diagnosed with atypical Parkinsonian Disorders was noted to be **248.71** ± 77.79 minutes (167.00-389.00 minutes). It was found to be longest in PSP patients, in whom the mean value was **274.50** ± 88.58 minutes (173.50-389.00 minutes).

In CBGD patients in our study, the mean value was **222.50** ± 78.49 minutes (167.00-278.00 minutes) compared to the CBGD patients in the study by *Roche et al* in which the mean value was **263** ±

138 minutes [35].

It was succeeded by the MSA patient in our study in whom the mean value was **198.00** minutes compared to a much higher value of **285.6** ± 51.96 minutes (194.00-343.00 minutes) in the MSA patients analysed by *Stanzani-Maserati et al* [70].

SLEEP EFFICIENCY (%)

Among the 7 patients of atypical Parkinsonian Disorders on whom PSG was performed, the mean value of sleep efficiency was **62.64** ± 10.83% (51.63-82.11%). It was found to be highest in PSP patients, in whom the mean value was **66.10** ± 12.51% (51.60-82.10%), which was much higher than that of *F. Sixel-Doring et al,* who in 2009, found a mean value of **43** ± 15% [73]. This difference is most likely attributable to the lesser duration of disease in our patients.

In CBGD patients, the mean value of sleep efficiency was **59.45** ± 10.45% (52.00-66.90%), which was quite high as compared to the study by *Roche et al* in which the mean value was **42** ± 22 % (52.00-66.90%) [35]. Mean value of sleep efficiency was lowest again in the MSA patient in whom it was **55.20**%, lower as compared to the study by *Stanzani-Maserati et al* in which the mean value was **72.7** ± 12.3 % (49.00-87.00%) [70].

N1 SLEEP PERCENTAGE (%)

The mean value of N1 sleep percentage in the 7 patients of atypical Parkinsonian Disorders who underwent PSG was **32.11** ± 22.82% (11.62-77.41%). It was yet again highest in PSP patients, in whom the mean value was **34.48** ± 30.40% (11.60-77.40%), which was roughly parallel to that of *F. Sixel-Doring et al,* who in 2009, found a mean value of **48.5** ± 19.7% in PSP patients [73].

It was closely followed by CBGD patients in whom the mean value was **32.85** ± 14.50% (22.60-43.10%);

N1 sleep percentage was least in our cohort in the MSA patient in whom the mean value was **21.20**% but almost triple the mean value of **7.2** % (3-20%) in the study by *Stanzani-Maserati et al* [70].

N2 SLEEP PERCENTAGE (%)

The mean value of N2 sleep percentage in the 7 patients of atypical Parkinsonian Disorders was observed to be **53.63** ± 18.49% (22.62-68.40%). It was highest in the MSA patient in whom the mean value was **61.20**%, higher as compared to the mean value of **46.3** % (27-72%) in the study by *Stanzani-Maserati et al* on MSA patients [70].

This was followed by the PSP patients in our cohort, in whom the mean value was **53.53** ± 20.77% (22.60-67.20%) which was almost double the value observed by *F. Sixel-Doring et al* in 2009, who found a mean value was **28.5** ± 18 % in their PSP patients [73].

N2 sleep percentage was lowest in the CBGD patients in whom the mean value was **50.05** ± 25.95% (31.70-68.40%).

N3 SLEEP PERCENTAGE (%)

Similarly, the mean value of N3 sleep percentage in the 7 patients of atypical Parkinsonian Disorders was **10.94** ± 8.96% (0-25.11%), which was maximum in the CBGD patients in whom it was **14.95** ± 14.35% (4.80-25.10%). This was in comparison to the study by *Roche et al* in which the mean value in CBGD patients was **27** ± 14 %[35].

This was followed by the MSA patient in our study in whom the mean value was **13.70**%, comparable to the mean value of **21.4** % (5-42%) in the study by *Stanzani-Maserati et al* in MSA patients [70].

N3 sleep percentage was minimum in the PSP patients in whom the mean value was noted to be **8.25** ± 8.30% (0.00-16.40%), almost four times that of *F. Sixel-Doring et al,* who had found a mean value of **2.5** ± 5.7 % in their PSP patients [73]. Thus, we can hypothesize that as the duration of disease increases in PSP, N2 as well as N3 sleep % decreases while N1 sleep % increases.

REM SLEEP PERCENTAGE (%)

In 3 out of the 7 patients of atypical Parkinsonian Disorders who underwent PSG, REM sleep was not attained. In the remaining 4 patients of atypical Parkinsonian Disorders who attained REM sleep,

the mean value of REM Sleep % was **3.30** ± 3.41% (0-8.10%).

The mean value was found to be **3.90** in the MSA patient in our study, much lower to the mean value of **25.2** % (9-51%) in the study by *Stanzani-Maserati et al* in MSA patients [70].

However, in the PSP patients, a mean value of **3.75** ± 4.36% (0-8.10%) was noted which was quite low as compared to study by *F. Sixel-Doring et al,* where REM sleep percentage was **20.5** ± 13 % in the PSP patients [73].

A mean value of **2.10** ± 2.97% (0-4.20%) was found in the CBGD patients in our cohort as compared to a much higher value of **10**% noted by *Roche et al* [35].

SLEEP LATENCY (MINUTES)

The mean value of sleep latency in the 7 patients diagnosed with atypical Parkinsonian Disorders was **19.71** ± 16.50 minutes (4.00-55.52 minutes), which was found to be longest in CBGD patients wherein the mean value was **36.95** ± 26.23 minutes (18.40-55.50 minutes). This difference was again most likely due to the lesser duration of disease in our lesser number of patients.

In PSP patients, the mean value of sleep latency was **12.88** ± 6.15 minutes (4.00-17.30 minutes), which was almost one-fifth as compared to that of *F. Sixel-Doring et al,* who in 2009, found a mean value of **61.9** ± 81.9 minutes in their PSP patients [73].

The mean value of sleep latency in our study population of atypical Parkinsonian Disorders was shortest in the MSA patient at **12.60** minutes compared to a similar value of **17.3** ± 13.22 minutes (2-47 minutes) in the MSA patients' group of *Stanzani-Maserati et al* [70].

REM LATENCY (MINUTES)

In the 4 patients diagnosed with atypical Parkinsonian Disorders who attained REM sleep on PSG, the mean value of REM latency was **115.93** ± 12.54 minutes (104.00-128.72 minutes). Amongst these, maximum latency was observed in the MSA patient, in whom the mean value was **128.70** minutes, compared to a similar value of **107.6** ± 63.7

minutes (21-254 minutes) in *Stanzani-Maserati et al* among their MSA patients [70].

This was closely succeeded by the CBGD patient wherein the mean value was **124.60** minutes. It was **105.20** ± 1.70 minutes (104.00-106.40 minutes) in our PSP patients' cohort, which was quite similar to that observed by *F. Sixel-Doring et al,* who observed d a REM sleep latency of **92.5** ± 106.7 minute in PSP patients [73].

APNOEA- HYPOPNEA INDEX (AHI)

Out the 7 patients diagnosed with atypical Parkinsonian Disorders who underwent PSG, the mean value of AHI was **8.12** ± 9.04(1.38-27.44) which was highest in the MSA patient with a mean value of **27.44**, quite high as compared to **9.00** ± 14.88 (0-50) observed by *Stanzani-Maserati et al* [70] in ten MSA patients.

However, it was substantially lower in the CBGD patients diagnosed with a mean value of **7.94** ± 2.16 (6.41-9.46). The mean value of AHI was **3.38** ± 2.75 (1.38-7.21) in the PSP patients, substantially lower than **24.6** ± 17.2 noted by *F. Sixel-Doring et al* in the cohort of PSP patients [73].

PERIODIC LEG MOVEMENT INDEX (PLMI)

The 7 patients of atypical Parkinsonian Disorders who underwent PSG had a mean value of PLMI of **29.24** ± 50.61(3.23-142.21), which was distributed as the highest in the PSP patients with mean value of **41.24** ± 67.37 (4.26-142.21) although substantially lower than **110.3 ± 79.9** noted by *F. Sixel-Doring et al* in their PSP patient's cohort [73].

PLMI had a mean value of **16.44** ± 18.67 (3.23-29.64) in the CBGD patients of our study population which was similar to **18.8** (0-77.1) noted by *Roche et al* in the cohort of CBGD patients they had observed [35].

SUMMARY AND CONCLUSION

1. Among the 52 patients who were studied and analysed, all the 23 patients who had been diagnosed with atypical Parkinsonian Disorders had sleep-related complaints (100%) compared to 76% in the PD group. All the 7 patients with no sleep-related complaints belonged to PD group. Thus, the incidence and prevalence of sleep-related dysfunction in our study group was uniformly high in both the groups. The mean age as well as disease duration was similar in both the disorder groups, making our results more credible.
2. To compare sleep dysfunctions between atypical Parkinsonian Disorders and Parkinson's Disease in the studied patient population, a total of 11 sleep-related complaints were considered. There were 5 complaints namely *insomnia*, *excessive daytime sleepiness, nocturia, irresistible urge to move legs* and *dream enacting behaviour,* which were found to be ***significantly higher*** in atypical Parkinsonian disorders patients as compared to patients of PD. Conversely, *mood disturbance* was noted to be ***significantly higher*** in PD patients. The rest of the sleep related complaints were not significant and two sleep-related complaints studied, namely, *sleep attacks and sleep-related injurious behaviour,* were absent in all the patients studied.
3. For the clinical scoring, 3 scales (ESS, PDSS-2 and RLS rating scale) were compared and analysed; all 3 of them were **significantly higher in** atypical Parkinsonian Disorders on comparing patients belonging to both groups, however a larger patient cohort is required to confirm these findings.
4. In Polysomnography (PSG), 12 parameters were assessed and compared across the total of 11 patients who underwent PSG. Three of the 12 parameters analysed, namely *total sleep time, sleep efficiency* and *REM sleep percentage* were **significantly lower** while *N1 sleep percentage* was **significantly higher** in atypical Parkinsonian Disorders. Thereby, a hypothesis emerges

from our study that these could be used in clinically ambiguous cases in which there is diagnostic dilemma to aid in the diagnosis of these patients. Thus, PSG is a useful clinical tool and this can be further consolidated by larger studies in the future.

5. Amongst the patients of atypical Parkinsonian Disorders, all of them had sleep-related complaints. The most common complaint in this group was also *insomnia. Excessive daytime sleepiness* and *breathing difficulty at night* were more common in MSA patients. *Early waking* was seen exclusively in PSP patients, while *nocturia* was more prevalent in these patients. *Irresistible urge to move legs* was more common in CBGD patients, while *dream enacting behaviour* was more commonly seen in DLB patients, seen in all of them. Three sleep-related complaints studied, namely, *cramps, sleep attacks and sleep related injurious behaviour,* were absent in all the atypical Parkinsonian Disorders patients studied.
6. For the Clinical scoring, *ESS* was highest in MSA and lowest in PSP patients while *PDSS-2* was highest in CBGD and lowest in PSP patients. Similarly, the *RLS rating scale* was highest in CBGD patients although least in MSA patients.
7. With regards to the PSG parameters amongst atypical Parkinsonian Disorders, total sleep time, sleep efficiency and N1 sleep percentage were lowest in MSA patients; N2 and REM sleep percentage were lowest in CBGD patients while N3 sleep percentage was lowest in PSP patients. Sleep latency was longest in CBGD patients while REM sleep latency was longest in MSA patients. AHI was maximum in MSA and PLMI was maximum in PSP patients.
8. Although our study provides head-on comparison between atypical Parkinsonian Disorders, a greater number of patients and larger studies are further required to consolidate our findings and to calculate p-values amongst disorders of this group.

LIMITATIONS

1. There was limited number of patients analysed across all disorders, partly because of the COVID-19 pandemic and partly because of the rarity of some of the disorders considered.
2. PSG was performed only on 11 of the 52 patients analysed, due to lack of consent by the patients and their caregivers, since it is an overnight procedure and required in-hospital admission.
3. PDSS-2 score was applied only on PD patients in all the studies in literature; however, in our cohort we had applied it to both PD and Atypical Parkinsonian Disorders' patients.
4. RLS rating scale was applied only on those with symptoms in the various compared but was applied uniformly across all patients in our study population, irrespective of them having symptoms related to RLS.

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S NO	MRD NO	AGE (in years)	SEX	DIAGNOSIS	H&Y SCALE	DURATION (IN YEARS)	COMPLAINT-INSOMNIA	EARLY WAKING	EXCESSIVE DAY TIME SLEEP	MOOD DIST	NOCTURIA	CRAMPS
1	657743	87	MALE	DLB		2	0	0	0	0	0	0
2	703256	39	FEMALE	PD	1	3	0	0	0	1	0	0
3	1046833	63	MALE	PD	2	2.5	1	1	0	0	0	0
4	1009980	62	FEMALE	PD	1	2	0	0	1	0	0	0
5	28889	78	MALE	PD	3	6	1	0	1	0	0	0
6	1115840	56	MALE	MSA		2	1	0	1	0	0	0
7	1014714	53	FEMALE	PD	1	3	0	0	0	0	0	0
8	484037	65	FEMALE	PD	2	2.5	0	1	0	1	0	0
9	906173	59	FEMALE	CBGD		2	1	0	0	0	0	0
10	1063899	67	MALE	PSP		2.5	1	0	0	0	1	0
11	307259	70	MALE	PD	2	3	0	0	1	1	0	0
12	383361	45	MALE	PD	1	2	0	0	0	0	0	0
13	146401	62	MALE	MSA		2	0	0	1	0	0	0
14	927868	60	MALE	PD	1	3	0	1	0	0	0	1
15	1151970	54	MALE	PD	1	2.5	1	0	0	0	0	0
16	159526	42	MALE	PD	1	2	0	0	0	0	0	0
17	390250	56	MALE	PSP		2.5	1	0	0	0	1	0
18	740936	68	MALE	CBGD		2	1	0	0	0	0	0
19	859211	70	MALE	DLB		2.5	1	0	1	0	0	0
20	333840	53	FEMALE	PD	2	3	1	1	0	0	0	0
21	1096072	65	MALE	PD	2	2.5	0	0	1	0	0	1
22	55236	46	MALE	PD	1	1.5	0	0	0	0	0	0
23	57792	52	MALE	PD	1	3	0	1	0	1	0	0
24	883776	69	FEMALE	PD	3	6	1	0	1	1	0	0
25	168508	56	MALE	PD	1	2	0	0	0	0	0	0
26	634523	72	MALE	MSA		3	1	0	1	0	0	0
27	672516	44	MALE	PD	1	2	0	0	0	0	0	1
28	401732	76	FEMALE	CBGD		2	1	0	0	0	0	0
29	888042	73	FEMALE	PSP		3	1	0	1	0	1	0
30	991954	66	MALE	DLB		2.5	1	0	0	0	0	0
31	75842	43	MALE	PD	1	3	0	0	0	1	0	0
32	1131396	75	MALE	PSP		2.5	1	0	1	0	0	0
33	930340	52	FEMALE	PD	2	2.5	0	0	0	0	0	0
34	42922	65	FEMALE	MSA		2.5	1	0	1	0	0	0
35	673118	71	MALE	PD	3	7	1	0	0	1	0	0
36	486144	70	MALE	DLB		2	0	0	1	0	0	0
37	818408	55	FEMALE	PD	1	3	0	1	0	0	0	0
38	64981	59	FEMALE	PSP		2	1	0	0	0	1	0
39	1230590	75	MALE	PD	2	3	0	0	1	0	0	0
40	1124298	32	FEMALE	PD	1	1	0	0	0	0	0	0
41	976021	54	MALE	PD	1	1	1	0	0	0	0	0
42	1026982	67	MALE	PSP		3	0	1	0	1	0	0
43	1038786	65	FEMALE	PSP		2	1	1	1	0	1	0
44	1044382	62	MALE	CBGD		2	1	0	1	0	1	0
45	1159031	62	FEMALE	PSP		1	0	0	0	0	1	0
46	1026614	64	MALE	PD	1	3	0	0	0	1	0	0
47	1062849	76	MALE	PD	2	1	0	1	0	0	0	0
48	750408	63	MALE	PD	1	2.5	0	0	0	0	0	1
49	1142398	59	MALE	PD	2	3	1	0	1	0	0	0
50	1141451	57	FEMALE	CBGD		2	0	0	0	0	1	0
51	913670	74	MALE	PSP		2.5	1	1	1	0	0	0
52	1177544	70	FEMALE	MSA		2	1	0	1	0	0	0

S NO	MRD NO	SLEEP ATTACKS	SLP REL. INJ BEH.	DREAM ENACN	IRRESISTIBLE URGE TO MOVE LEGS	BREATHING DIFF. AT NIGHT	ESS SCORE	PDSS 2 SCORE	RLS SCALE	LEVODOPA DOSE (mg)	LEVODOPA EQUIV. DOSE (mg)	SLEEP STUDY DONE
1	657743	0	0	1	1	0	13	22	19	300	450	0
2	703256	0	0	0	0	0	5	12	3	300	338	0
3	1046833	0	0	0	0	0	12	17	4	300	450	0
4	1009980	0	0	0	0	0	16	20	7	300	300	0
5	28889	0	0	0	0	0	17	21	8	600	838	0
6	1115840	0	0	0	0	1	16	20	7	300	375	0
7	1014714	0	0	0	0	0	7	11	2	150	150	0
8	484037	0	0	0	0	0	11	16	6	300	375	0
9	906173	0	0	0	1	0	13	20	18	300	450	0
10	1063899	0	0	0	0	0	12	17	9	400	550	0
11	307259	0	0	0	0	0	14	20	5	600	600	0
12	383361	0	0	0	0	0	4	6	1	300	338	0
13	146401	0	0	0	0	1	16	19	6	600	700	0
14	927868	0	0	0	0	0	9	17	4	300	300	0
15	1151970	0	0	0	0	0	7	12	2	0	76	0
16	159526	0	0	0	0	0	3	5	1	150	150	0
17	390250	0	0	0	0	0	8	14	2	450	450	0
18	740936	0	0	0	1	0	12	18	22	600	676	0
19	859211	0	0	1	0	0	15	19	8	450	488	0
20	333840	0	0	0	0	0	10	18	3	600	600	0
21	1096072	0	0	0	0	0	14	19	9	450	600	0
22	55236	0	0	0	0	0	4	5	1	150	150	0
23	57792	0	0	0	0	0	9	17	7	600	750	0
24	883776	0	0	0	0	0	16	23	8	750	900	0
25	168508	0	0	0	0	0	5	9	2	300	300	0
26	634523	0	0	0	0	1	15	22	6	450	526	0
27	672516	0	0	0	0	0	8	10	6	300	338	0
28	401732	0	0	0	1	0	10	21	18	600	675	0
29	888042	0	0	0	0	0	12	16	8	450	450	0
30	991954	0	0	1	0	0	13	20	11	500	600	0
31	75842	0	0	0	0	0	8	9	2	300	300	0
32	1131396	0	0	0	0	0	15	18	5	400	538	0
33	930340	0	0	0	0	0	4	7	0	450	450	0
34	42922	0	0	0	0	1	12	14	3	600	700	0
35	673118	0	0	0	0	1	10	19	6	875	975	0
36	486144	0	0	1	1	0	13	20	24	600	600	0
37	818408	0	0	0	0	0	7	12	6	400	400	0
38	64981	0	0	0	0	0	6	14	2	450	488	0
39	1230590	0	0	0	0	1	11	17	4	600	700	0
40	1124298	0	0	0	0	0	2	3	0	150	150	0
41	976021	0	0	0	0	0	4	6	2	300	400	0
42	1026982	0	0	0	1	0	9	21	23	600	675	1
43	1038786	0	0	0	0	0	16	24	7	500	638	1
44	1044382	0	0	0	0	0	15	19	5	450	550	1
45	1159031	0	0	0	0	0	4	10	2	600	700	1
46	1026614	0	0	0	0	0	6	9	3	600	600	1
47	1062849	0	0	0	0	1	9	16	4	450	450	1
48	750408	0	0	0	0	1	4	12	3	500	600	1
49	1142398	0	0	0	0	0	15	22	4	600	700	1
50	1141451	0	0	1	1	0	12	24	19	450	488	1
51	913670	0	0	0	0	0	11	14	3	600	700	1
52	1177544	0	0	1	0	1	16	22	7	450	525	1

S NO	MRD NO	AGE (in years)	SEX	DIAGNOSIS	H&Y SCALE	DURATION (IN YEARS)	COMPLAINT-INSOMNIA	EARLY WAKING	EXCESSIVE DAY TIME SLEEP	MOOD DIST	NOCTURIA	CRAMPS	SLEEP ATTACKS	SLP REL. INJ BEH.	DREAM ENACN	IRRESISTIBLE URGE TO MOVE LEGS	BREATHING DIFF. AT NIGHT	ESS SCORE	PDSS 2 SCORE
1	1026982	67	MALE	PSP		3	0	1	0	1	0	0	0	0	0	1	0	9	21
2	1038786	65	FEMALE	PSP		2	1	1	1	0	1	0	0	0	0	0	0	16	24
3	1044382	62	MALE	CBGD		2	1	0	1	0	1	0	0	0	0	0	0	15	19
4	1159031	62	FEMALE	PSP		1	0	0	0	0	1	0	0	0	0	0	0	4	10
5	1026614	64	MALE	PD	1	3	0	0	0	1	0	0	0	0	0	0	0	6	9
6	1062849	76	MALE	PD	2	1	0	1	0	0	0	0	0	0	0	0	1	9	16
7	750408	63	MALE	PD	1	2.5	0	0	0	0	0	1	0	0	0	0	1	4	12
8	1142398	59	MALE	PD	2	3	1	0	1	0	0	0	0	0	0	0	0	15	22
9	1141451	57	FEMALE	CBGD		2	0	0	0	0	1	0	0	0	1	1	0	12	24
10	913670	74	MALE	PSP		2.5	1	1	1	0	0	0	0	0	0	0	0	11	14
11	1177544	70	FEMALE	MSA		2	1	0	1	0	0	0	0	0	1	0	1	16	22

S NO	MRD NO	RLS SCALE	LEVODOPA DOSE	LEVODOPA EQUIV. DOSE	SLEEP STUDY DONE	TOTAL SLP TIME (mins)	SLEEP EFFICIENCY (%)	N1 SLEEP %	N2 SLEEP %	N3 SLEEP %	REM SLEEP %	SLEEP LATENCY (mins)	REM SLEEP ATTAINED	REM LATENCY (mins)	AHI	PLMI	AVG SaO2 (%)	MIN Sa02 (%)
1	1026982	23	600	675	1	389	82.1	77.4	22.6	0	0	4	0		1.39	142.21	98	94
2	1038786	7	500	638	1	173.5	51.6	34.6	63.1	2.3	0	13.5	0		1.38	7.61	96	87
3	1044382	5	450	550	1	167	52	43.1	31.7	25.1	0	55.5	0		9.46	3.23	97	89
4	1159031	2	600	700	1	276	66.3	11.6	67.2	14.3	6.9	17.3	1	104	7.21	4.26	96	92
5	1026614	3	600	600	1	402	83.4	5.2	56.3	20.2	18.3	9.2	1	93.4	4.83	7.15	97	89
6	1062849	4	450	450	1	282	78.2	7.3	63.4	16.5	12.8	16.8	1	106.1	11.23	5.04	93	81
7	750408	3	500	600	1	394	84.5	6.8	62.7	16.9	13.6	11.7	1	92.6	18.76	5.2	92	80
8	1142398	4	600	700	1	362	79.3	18.4	54.7	14.5	12.4	17.3	1	105.2	8.81	4.87	94	92
9	1141451	19	450	488	1	278	66.9	22.6	68.4	4.8	4.2	18.4	1	124.6	6.41	29.64	95	90
10	913670	3	600	700	1	259.5	64.4	14.3	61.2	16.4	8.1	16.7	1	106.4	3.52	10.87	94	91
11	1177544	7	450	525	1	198	55.2	21.2	61.2	13.7	3.9	12.6	1	128.7	27.44	6.83	92	84

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Date 8/9/21

The Principal,
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Subject: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 22.01.2021 has approved the plan of thesis of Dr Parth Bansal, a student of your college for DM Neurology along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
To study the spectrum of sleep dysfunction across the atypical parkinsonian disorders and parkinson's disease

Supervisor
Dr. Rajinder Bansal
Prof.,
Dept. of Neurology,
DMCH, Ludhiana.

Co-Supervisor
Dr. Birinder Singh Paul
Prof.,
Dept. of Neurology,
DMCH, Ludhiana.

The student has to submit the three copies of thesis (along with PDF format), to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

12. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

NEUROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

MARCH, 2020

DR. PARTH BANSAL

DEPARTMENT OF NEUROLOGY
DAYANAND MEDICAL COLLEGE & HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE
For the degree of	D.M Neurology
Name of the candidate	Dr. Parth Bansal
Supervisor	Dr. Rajinder Bansal, Professor, Department of Neurology, DMCH, Ludhiana
Co-supervisor	Dr. Birinder Singh Paul, Professor, Department of Neurology, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Sleep disturbances are among the most common nonmotor symptoms ranging from approximately 40% to 90% in PD patients[2]. In contrast to PD, sleep disorders in atypical parkinsonian syndromes have not been systematically studied.

Aim of Study: Our aim is to know the incidence, prevalence and to compare sleep dysfunctions in Indian patients with atypical parkinsonian disorders and parkinson's disease

Materials & Methods: This cross-sectional, non-blinded study will be conducted on follow up and newly diagnosed patients presenting to Neurology department DMCH Ludhiana between 1st March 2020 to 31st December 2021 after taking informed and written consent.

Clinical Significance: Sleep dysfucntions can influence treatment outcome and morbidity in PD and atypical parkinsonian disorders patients

Keywords: SLEEP DYSFUCNTIONS, ATYPICAL PARKINSONIAN DISORDERS, PARKINSON'S DISEASE

(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE"** exist in the Department of Cardiology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself/herself under our supervision and guidance.

Supervisor

Dr. Rajinder Bansal
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Name of candidate	Dr. Parth Bansal
Department	Neurology
Topic of Thesis	TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE
Likely date of appearing in PG examination	MAY, 2022
Date of enrollment	10-09-2019
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PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	DR. PARTH BANSAL Bansal Nursing Home, Railway Road, Tohana Dist. Fatehabad, Haryana- 125120
2	NAME OF THE INSTITUTE	DAYANAND MEDICAL COLLEGE AND HOSPITAL LUDHIANA
3	COURSE OF STUDY AND SUBJECT	DM NEUROLOGY
4	DATE OF ADMISSION OF COURSE	10-09-2019
5	TITLE OF THE TOPIC	TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE

6 BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Parkinson's disease (PD) is a movement disorder characterized by bradykinesia, resting tremors, rigidity, and impaired postural reflexes, which are caused by the degeneration of dopaminergic neurons in the substantia nigra.[1] Serotoninergic, noradrenergic, and cholinergic systems systems may play a role in the development of the nonmotor symptoms. Sleep disturbances are among the most common nonmotor symptoms, with a prevalence ranging from approximately 40% to 90%.[2]

Spectrum of sleep disorders associated with parkinson's disease :

1. *REM Sleep Behavior Disorder (RBD):* In the Braak schema, involvement of the pathologic process in PD affects the SLD (sublaterodorsal nucleus), the magnocellular reticular formation (MCRF), and the perilocus coeruleus alpha structures as early as Stage 2. RBD is characterized by persistence of muscle tone during REM sleep accompanied by motor/behavioral activity and dreaming.[3]
2. *Excessive Daytime Sleepiness:* Excessive daytime sleepiness, defined as inappropriate and undesirable sleepiness during waking hours, is one of the most commonly reported sleep complaints in patients with PD, affecting between 15% and 50% of PD patients. The degree of EDS has been shown to be a key determinant of these patients' quality of life . The severity of EDS in patients with PD has been shown to increase with disease severity and disease duration.[4]
3. *Restless Legs Syndrome and Periodic Limb Movements:* Restless legs syndrome (RLS) is a common neurologic disorder that affects 4%–10% of the general population. The pathophysiolog is not clear-cut but it has been associated with iron deficiency and impairment of cerebral dopaminergic systems. The generally accepted frequency is 10%–20% association of RLS symptoms in patients with PD.[5]

4. *REM Sleep and Hallucinations:* F˙enelon et al. showed that three factors were independently predictive of visual hallucinations: severe cognitive impairment, duration of PD, and daytime sleepiness. The association of RBD has been found to increase the risk of hallucinations by a factor of 3.[6]
5. *Sleep-Disordered Breathing:* The reported frequency of sleep-disordered breathing (SDB) in PD varies from 20% to 60%. Possible etiologic explanations include decrease in upper airway muscle tone because of degeneration of the brainstem serotoninergic neurons that innervate the muscles of the upper airway, deficient respiratory muscle coordination, or autonomic dysregulation.[7]

Spectrum of Sleep disorders associated with atypical Parkinsonian disorders: In contrast to PD, sleep disorders in atypical parkinsonian syndromes, such as Multiple system atrophy (MSA), dementia with Lewy Bodies (DLB), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), have not been systematically studied. Sleep dysfunction can frequently be observed in these patient populations.

1. **Multiple system atrophy (MSA)** is a neurodegenerative disorder characterized by a combination of autonomic dysfunction, parkinsonism, and/or ataxia. Obstructive sleep apnea (OSA) can be observed, but there are also case reports of central apneas occurring as the first symptom of MSA. Nocturnal stridor is one of the most serious sleep disorders associated with MSA.[8]
   Excessive daytime sleepiness (EDS) has been reported in 28% of Caucasian patients with MSA and 24% of Japanese patients with MSA. One of the hallmark symptoms of MSA is a loss of the normal nocturnal dip in blood pressure which appears to be much more pronounced in patients with MSA, compared to PD.[9,10]
2. **Dementia with Lewy Bodies (DLB)** - the strong association between RBD and DLB prompted the inclusion of RBD as a core clinical feature for the diagnosis of DLB in 2011.Excessive daytime sleepiness is seen in 75% cases of DLB.[11]

3. **Progressive supranuclear palsy (PSP)** - PSP patients has significantly decreased total sleep time and REM sleep, along with a significant increase in the number and duration of nocturnal awakenings. REM sleep without atonia and RBD are seen in 33% of PSP patients.[12]
4. **Cortico basalde generation (CBD)** – Sleep disorders in CBD patients includes insomnia, periodic limb movements during sleep, sleep disordered breathing. Interestingly, periodic limb movements are seen more severe on the side dominantly affected by parkinsonism.[13]

6.2 REVIEW OF LITERATURE

A study conducted by Turner RS in 2002 showed that Idiopathic rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia clinically linked with the alpha-synucleinopathies multiple systems atrophy (MSA), Parkinson's disease (PD), and dementia with Lewy bodies (DLB). Available autopsy information is limited but suggests that the pathologic basis of idiopathic RBD may be neuronal loss and Lewy bodies in pigmented monoaminergic nuclei, including the locus coeruleus and substantia nigra, which project to pontine nuclei mediating atonia during REM sleep. Thus, idiopathic RBD may be an alpha-synucleinopathy per se and a harbinger of impending PD, DLB, or MSA.[14]

Another study conducted by Nihon Rinsho in 2004 showed that approximately 74-94% patients with Parkinson's disease have sleep disorders: such as frequent awakening, excessive daytime sleepiness, nightmares, nocturnal cramps, REM sleep behavior disorders and so on. In contrast, the relationship between physiological mechanism of sleep and the dopamine systems are still obscure, because the dopamine systems are not directly related neither initiating or maintaining sleep system nor awaking system. However, most of all the dopaminergic drugs were reported to induce sleepiness or sleep attacks in the patients with Parkinson's disease.[15]

Another study conducted by De Cock VC et al in 2008 showed that altered sleep and vigilance are among the most frequent symptoms, besides parkinsonism, in movement disorders. As many as 60% of patients with Parkinson's disease (PD) experience insomnia, 15-59% show rapid eye movement (REM) sleep behavior disorders (RBDs), and 30% show excessive daytime sleepiness RBDs are thought to be caused by lesions in the REM sleep atonia system, and can, in association with other early markers of neurodegenerative diseases, such as olfactory, cognitive and autonomic disturbances, precede parkinsonism by several years. Daytime sleepiness, often with a narcolepsy-like phenotype, is a common occurrence in PD, owing to lesions in the arousal systems of the brain. The use of dopamine

agonists increases the risk of sleep attacks, especially when driving, suggesting a drug-disease interaction.[16]

Another study conducted by Arnulf I et al in 2009 showed that excessive daytime sleepiness is a disabling and vital problem in patients with PD. It affects around 33% patients and culminates in sleep attacks (without prodroma) in 1 to 4% of the patients. When monitored, short, narcolepsy-like naps with abnormal intrusion of REM sleep during daytime (and hypnagogic hallucinations as wakeful dreams) are observed in 33-41% patients, while other patients display naps with non REM sleep. Although insomnia, sleep apnea and periodic leg movements are common in these patients, there is no clear link between the night events and the level of sleepiness. Patients treated with dopamine agonists are two to three fold more exposed to sleep attacks than those on levodopa, with large variability between patients. Sleepiness may exist, to a lesser degree, before the onset of parkinsonism and before the use of dopamine agents, suggesting that other, disease-dependant factors contribute to the sleepiness.[17]

Another study conducted by Nomura T et al in 2012 showed that PSP patients had more severe symptoms of Parkinsonism and cognitive impairment, and took lower doses of dopaminergic agents compared with PD patients. The PSP group had lower values for both estimated total sleep time and sleep efficiency on PSG compared with the PD group ($p = 0.002$, $p = 0.021$, respectively). The PSP group also included a significantly smaller number of patients having REM sleep without atonia (RWA) compared with the PD group ($n = 5$, 20.0% vs. $n = 56$, 60.2%, $p = 0.003$). None of the PSP patients were experiencing RBD-related symptoms at the time of the investigation, while 30 PD patients (32.3%) had RBD-related symptoms.[18]

Another study conducted by Sabra M. Abbott et al in 2014 showed that Sleep disorders are commonly observed in atypical arkinsonism, with particular disorders occurring more frequently in specific parkinsonian disorders. Multiple system atrophy (MSA) is a synucleinopathy often associated with nocturnal stridor, which is a

serious, but treatable, condition highly specific to MSA. In addition, this disorder is strongly associated with rapid eye movement sleep behavior disorder (RBD), which is also observed in dementia with Lewy bodies. RBD is far less prevalent in progressive supranuclear palsy (PSP), which is a tauopathy. Insomnia and impaired sleep architecture are the most common sleep abnormalities observed in PSP. Corticobasilar degeneration is also a tauopathy, but has far fewer sleep complaints associated with it than PSP.[19]

Another study conducted by Koo DL et al in 2018 showed that Among the 92 patients with RBD, 35 had iRBD, 25 had PD-RBD, 17 had MSA-RBD, and 15 had DLB-RBD. The mean apnea-hypopnea index of atypical parkinsonism with RBD (AP-RBD) group was 16.2 ± 17.7 events/h (MSA-RBD, 14.0 ± 16.6; DLB-RBD, 18.8 ± 19.1), which was significantly higher than the other groups ($p < 0.05$). The proportion of patients with 100% supine sleep in the AP-RBD group (44%) was higher than that in the iRBD group (14%; $p = 0.030$). The proportion of OSA with 100% supine sleep position was significantly higher in the MSA-RBD and DLB-RBD groups than in the iRBD group ($p = 0.042$ and $p = 0.029$, respectively).[20]

6.3 AIMS AND OBJECTIVES OF THE STUDY

- To study incidence and prevalence of sleep dysfunctions in Indian patients with atypical parkinsonian disorders and parkinson's disease.
- To compare sleep dysfunctions between atypical parkinsonian disorders and parkinson's disease in Indian patients.
- To compare sleep dysfunctions among various types of atypical parkinsonian disorders.

7.0 MATERIALS AND METHODS

This cross-sectional, non-blinded study will be conducted to know the various sleep dysfunctions in Indian patients with atypical parkinsonian disorders and parkinson's disease. All follow up and newly diagnosed patients presenting to Neurology department DMCH Ludhiana between 1st March 2020 to 30th June 2021 will be enrolled for study after taking informed and written consent.

7.1 SOURCE OF DATA:

Data collection will be done by analyzing the patients with atypical parkinsonian disorders and parkinson's disease presenting to Neurology department DMC & HOSPITAL.

7.2 METHOD OF COLLECTION OF DATA

Any patient who present to DMCH in patient/ out patient clinic who have:

1. Age 18 years or above
2. Clinical diagnosis of Parkinson's disease using UK Parkinsons Disease Brain Bank criteria[21]

Step 1: Diagnosis of parkinsonian syndrome • bradykinesia • 1 or more of: - rigidity - rest tremor - postural instability
Step 2: Absence of the following exclusion criteria • repeated strokes with stepwise progression of parkinsonism • history of repeated head injury • history of definite encephalitis • oculogyric crises • neuroleptic treatment at symptom onset • more than one affected relative • sustained remission of symptoms • strictly unilateral features after 3 years • supranuclear gaze palsy • cerebellar signs • early severe autonomic involvement • early severe dementia with disturbances of memory, language, and praxis • Babinski sign • presence of cerebral tumour or communicating hydrocephalus on brain imaging • negative response to large doses of levodopa in absence of malabsorption • MPTP exposure
Step 3: Supportive criteria for Parkinson's disease – 3 or more of the following required • unilateral onset • rest tremor present • progressive disorder • persistent asymmetry affecting side of onset most • excellent response (70-100%) to levodopa • severe levodopa-induced chorea • levodopa response for 5 years or more • clinical course of 10 years or more

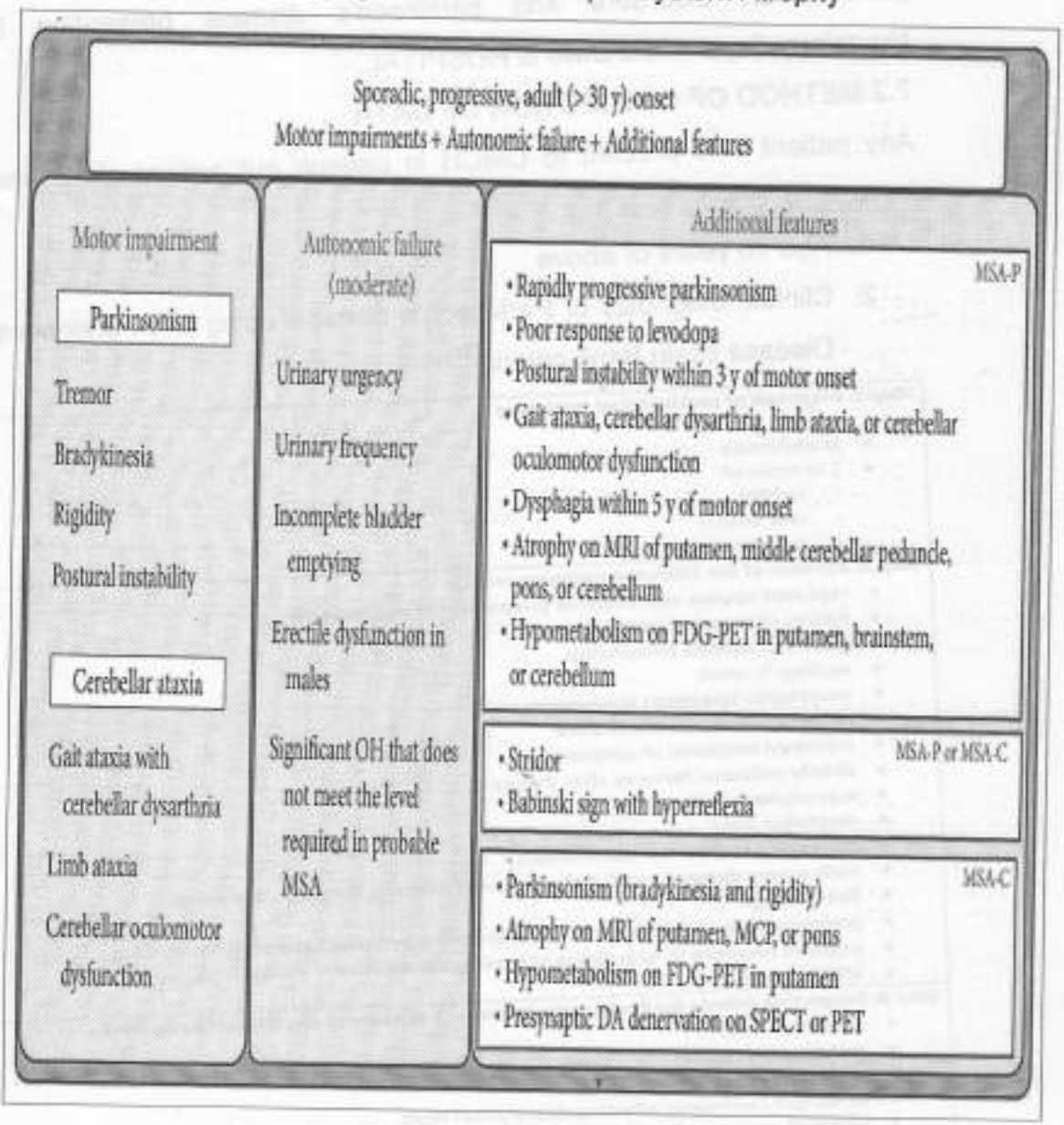
3. Features of possible or probable Progressive Supranuclear Palsy defined as[12] :

Probable PSP : vertical supranuclear palsy and prominent postural instability with falls within 1st year of disease onset

Possible PSP : either vertical supranuclear palsy or both (1) slowing of vertical saccades and (2) postural instability with falls within 1st year of disease onset

For both possible and probable PSP disease onset should be at age of 40 or later and the disorder should be progressive in nature

4. Clinical and Imaging features of Multiple System Atrophy[8]


Sporadic, progressive, adult (> 30 y)-onset
Motor impairments + Autonomic failure + Additional features
Motor impairment
Parkinsonism
Tremor
Bradykinesia
Rigidity
Postural instability
Cerebellar ataxia
Gait ataxia with cerebellar dysarthria
Limb ataxia
Cerebellar oculomotor dysfunction
Autonomic failure (moderate)
Urinary urgency
Urinary frequency
Incomplete bladder emptying
Erectile dysfunction in males
Significant OH that does not meet the level required in probable MSA
Additional features
MSA-P
• Rapidly progressive parkinsonism
• Poor response to levodopa
• Postural instability within 3 y of motor onset
• Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
• Dysphagia within 5 y of motor onset
• Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
• Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
MSA-P or MSA-C
• Stridor
• Babinski sign with hyperreflexia
MSA-C
• Parkinsonism (bradykinesia and rigidity)
• Atrophy on MRI of putamen, MCP, or pons
• Hypometabolism on FDG-PET in putamen
• Presynaptic DA denervation on SPECT or PET

5. Features of Dementia with Lewy Bodies[11]

Diagnosis Requires

- ≥ 2 core features or
- 1 core feature plus 1 suggestive feature

Core Features

- Fluctuating cognition
- Recurrent visual hallucinations
- Parkinsonism

Suggestive Features

- REM sleep behavior disorder
- Severe neuroleptic sensitivity
- Low dopamine activity in basal ganglia on dopamine transporter SPECT or PET

6. Features of Corticobasal Ganglionic Degeneration defined as[13]

:

Corticobasal Degeneration (CBD) criteria

Core Features	Supportive Features
Cortical dysfunction – Asymmetric ideomotor apraxia – Alien limb phenomenon – Visual or sensory hemineglect – Focal or asymmetric myoclonus – Non-fluent aphasia (overlap with PNFA) Extrapyramidal dysfunction – Asymmetric rigidity lacking sustained levodopa response, and focal dystonia	• Lateralized cognitive dysfunction with preserved memory and learning • MRI with asymmetric atrophy in parietal and frontal cortex • FDG-PET decreased glucose uptake in parietal and frontal cortex, basal ganglia and thalamus.

7. Patients of atypical parkinsonian disorders and parkinson's disease will be subjected to Sleep Questionnaires including
    a. Epworth Sleep Scale
    b. Parkinson's Disease Sleep Scale-2
    c. Restless Leg Syndrome Rating Scale (if required)
8. Exclusion criteria
    a. Patients on Sleep medications
    b. Diabetes Mellitus
    c. Hypothyroidism
    d. Drug induced Parkinsonism
    e. Vascular Parkinson's disease

OUTCOME: Incidence and prevalence of sleep dysfunctions in Parkinson's disease and Atypical Parkinsonian disorders and comparison of various sleep dysfunctions among them

STATISTICAL ANALYSIS: Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups will be done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and exact test will be used when the expected frequency is less than 5. A probability value (p value)less than 0.05 will be considered statistically significant. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

NO

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

ATTACHED HEREWITH

8.0 LIST OF REFERENCES

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PROFORMA

Name: Sr. No

Age:

Sex:

MRD. No.

Address:

Chief complaints:

- Insomnia
- Early waking
- Excessive daytime sleeping
- Loss of energy
- Mood disturbances
- Memory impairment
- Nocturia
- Cramps
- Sleep attacks
- Sleep related injurious behavior
- Dream enacting behavior
- Irresistible urge to move legs

Brief History of Present illness

Diagnosis-

Past History

- Hypothyroidism
- Diabetes Mellitus
- Depression
- History of primary sleep disorders (Parasomnias or Dyssomnias)
- Any surgical h/o:

Signature of Candidate

Signature of Supervisor

Personal History

Smoker/Non Smoker:

Alcoholic/Non-Alcoholic:

Tobacco addict:

Veg. / non veg:

Family History

Diabetes Mellitus:

Hypertension:

CVA:

Parkinsonism:

Examination

GPE

Cyanosis :

Jaundice :

Oedema :

Pulse :

Blood Pressure :

Respiratory Rate:

Temperature :

System Examination

-CNS

1. Higher mental function

a. Consciousness

b. Oriented to time / place and person

c. Attention / calculation

d. Recall

e. Language

2. Cranial nerves

Signature of Candidate

Signature of Supervisor

3. **Motor System**

a. Position / attitude of limbs

b. Bulk (wasting / hypertrophy)

c. Tone (Spasticity / flaccidity)

d. Power

e. Deep tendon reflexes

f. Superficial reflexes

4. **Sensory System:**

a. Superficial sensations
b. Deep sensations
c. Rhomberg's sign

5. **Cerebellum**

6. **Gait and Stance**

Signature of Candidate

Signature of Supervisor

Sleep Questionnaires

1. **Epworth Sleep Scale**[22]

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations?
Use the following scale to choose the most appropriate number:

0 no chance	1 slight chance	2 moderate chance	3 high chance
Sitting and reading			0 1 2 3
Watching television			0 1 2 3
Sitting inactive, in a public space			0 1 2 3
Lying down to rest in the afternoon when circumstances permit			0 1 2 3
Sitting and talking to someone			0 1 2 3
Sitting quietly after a lunch without alcohol			0 1 2 3
As a passenger in car for an hour without a break			0 1 2 3
In a car, while stopped for a few minutes in traffic			0 1 2 3

Total Score:

2. Parkinson's Disease Sleep Scale-2[23]

Please rate the severity of the following based on your experiences during the past week (7 days). Please make a cross in the answer box

	Very often (This means 6 to 7 days a week)	Often (This means 4 to 5 days a week)	Sometimes (This means 2 to 3 days a week)	Occasionally (This means 1 day a week)	Never
1) Overall, did you sleep well during the last week?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2) Did you have difficulty falling asleep each night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3) Did you have difficulty staying asleep?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4) Did you have restlessness of legs or arms at nights causing disruption of sleep?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5) Was your sleep disturbed due to an urge to move your legs or arms?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
6) Did you suffer from distressing dreams at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
7) Did you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
8) Did you get up at night to pass urine?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
9) Did you feel uncomfortable at night because you were unable to turn around in bed or move due to immobility?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
10) Did you feel pain in your arms or legs which woke you up from sleep at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
11) Did you have muscle cramps in your arms or legs which woke you up whilst sleeping at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
12) Did you wake early in the morning with painful posturing of arms and legs?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
13) On waking, did you experience tremor?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
14) Did you feel tired and sleepy after waking in the morning?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
15) Did you wake up at night due to snoring or difficulties with breathing?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Signature of Candidate

Signature of Supervisor

3. Restless Leg Syndrome Rating Scale (if required)[24]

Restless Legs Syndrome Rating Scale

Have the patient rate his/her symptoms for the following ten questions.
The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions.
The examiner should mark the patient's answers on the form.

In the past week... (1) Overall, how would you rate the RLS discomfort in your legs or arms? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None	In the past week... (6) How severe was your RLS as a whole? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None
In the past week... (2) Overall, how would you rate the need to move around because of your RLS symptoms? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None	In the past week... (7) How often did you get RLS symptoms? _ (4) Very often (6 to 7 days in 1 week) _ (3) Often (4 to 5 days in 1 week) _ (2) Sometimes (2 to 3 days in 1 week) _ (1) Occasionally (1 day in 1 week) _ (0) Never
In the past week... (3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around? _ (4) No relief _ (3) Mild relief _ (2) Moderate relief _ (1) Either complete or almost complete relief _ (0) No RLS symptoms to be relieved	In the past week... (8) When you had RLS symptoms, how severe were they on average? _ (4) Very severe (8 hours or more per 24 hour) _ (3) Severe (8 to 6 hours per 24 hour) _ (2) Moderate (1 to 3 hours per 24 hour) _ (1) Mild (less than 1 hour per 24 hour) _ (0) None
In the past week... (4) How severe was your sleep disturbance due to your RLS symptoms? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None	In the past week... (9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None
In the past week... (5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None	In the past week... (10) How severe was your mood disturbance due to your RLS symptoms - for example angry, depressed, sad, anxious or irritable? _ (4) Very severe _ (3) Severe _ (2) Moderate _ (1) Mild _ (0) None
Sum of scores =	
Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)	
1. Answers for this IRLS are scored from 4 for the first (top) answer (usually "very severe") to 0 for the last answer (usually none). All items are scored. The sum of the item scores serves as the scale score. The International Restless Legs Syndrome Study Group holds the copyright for this scale.	

Signature of Candidate

Signature of Supervisor

RADIOLOGICAL INVESTIGATIONS (if required)

MRI Brain

CT Head

Other investigation

Polysomnography (wherever feasible)[25]

Parameters of polysomnography :

Assessment of sleep stages requires 3 studies: electroencephalography (EEG), electrooculography (EOG), and surface electromyography (EMG).

Other parameters that can be monitored in a sleep study include the following:

- Electrocardiography
- Pulse oximetry
- Respiratory effort (thoracic and abdominal)
- Sound recordings to measure snoring
- Surface EMG monitoring of limb muscles (to detect limb movements, periodic or other)
- Continuous video monitoring

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o..... .....am willing to participate in the study **"TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____

गवाह के हस्ताक्षर

नाम:

_____

रोगी के हस्ताक्षर/अंगूठे का निशान

नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"TO STUDY THE SPECTRUM OF SLEEP DYSFUNCTION ACROSS THE ATYPICAL PARKINSONIAN DISORDERS AND PARKINSON'S DISEASE" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____
ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ

_____
ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਮਿਤੀ_____

ਪਤਾ _____

ਪਤਾ _____

_____
ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____
ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ